Prophylactic Treatment of Factor VIII Deficiency

By Richard J. Hirschman, Samuel B. Itscoitz, and N. Raphael Shulman

Spontaneous bleeding episodes and hemorrhage following surgery or trauma in hemophilia can be treated readily with the potent Factor VIII concentrates now available. However, requirements for long-term prophylactic therapy to prevent hemarthroses and other spontaneous hemorrhages have not been clearly defined. Three reports of prophylactic therapy in hemophilia employing widely differing regimens have appeared: a preliminary report on the use of cryoprecipitate over a six-month period in one patient, an abstract on the use of a commercial Factor VIII concentrate for three months, and a paper describing the prophylactic use of a Factor VIII concentrate in a patient for one year.

It is the purpose of this paper to report our experience with prophylactic treatment of four patients for periods up to two years. Two of the patients had classical hemophilia and two were twins with an unusual combination of classical hemophilia and von Willebrand's disease. All had frequent spontaneous hemorrhages. Cryoprecipitate given on a convenient schedule was found to provide adequate Factor VIII to significantly decrease spontaneous hemorrhages. In one patient, the progressive enlargement of an extensive iliac pseudotumor was arrested for a two-year period. Complications of prolonged prophylactic therapy were minimal.

Materials and Methods

Cryoprecipitate rich in Factor VIII was prepared and stored by a modification of Pool's technique. Factor VIII concentration of infusates varied from approximately 500-600 per cent (5-6 Units/ml) of the average normal value. The supernatant plasma from which the cryoprecipitate had been removed, containing less than 0.5 Units/ml., was used for control infusions in Cases II, III and IV. The volume of Factor VIII deficient plasma corresponded to the volume of cryoprecipitate used.

Factor VIII levels were measured by the partial thromboplastin technique, using 3.8 per cent inosithin and human Factor VIII deficient plasma, and by the method of Shulman et al. to measure minimal concentrations of Factor VIII. Ortho plasma coagulation control was used as a standard.

Bleeding times were performed by the method of Ivy et al.

Case Reports and Results

Case I. (D.K., NIH #07-20-98)

This 34-year-old male severe classical hemophiliac had typical recurrent hemarthroses, easy bruising, and dental bleeding, as well as retroperitoneal hemorrhage in childhood. At the age of 15, hemorrhage following extraction of six teeth lasted 40 days and required 30 blood transfusions. At the age of 23, foot drop resulted from bleeding into the area of...
the left peroneal nerve. At the age of 24, a lytic lesion in the left iliac crest associated with a mass on the left side of the abdomen was diagnosed as pseudotumor. The pseudotumor progressively enlarged over the ensuing nine years until it filled the left lower quadrant and extended to within two fingerbreadths of the left costal margin. A five-by-eight-inch portion of this rock-hard mass protruded laterally beyond the ilium when the patient was first seen at the National Institutes of Health. At that time, he was also having one to two incapacitating hemarthroses per month. Intensive cryoprecipitate therapy was started immediately and has been continued for over two years. The different dose schedules used and their effects on hemorrhagic episodes are summarized in Table 1. When Factor VIII levels were maintained above 1 per cent, a dramatic decrease in the frequency of hemarthroses occurred and the patient’s mental outlook was greatly improved. In the two-year period of prophylactic therapy, the palpable diameter of the pseudotumor has decreased by about three inches, although x-rays of the lytic lesion in the ilium have not changed. Throughout this time the patient has been active and working regularly as a physician in a University medical center.

Case II. (R.E., NIH #00-95-44)

This 34-year-old male classical hemophiliac had the usual recurrent symptoms of hematuria, hemarthrosis and excessive bleeding from minor injuries. In 1964, the incidence of hemarthroses in the shoulders, elbows, wrists, knees and ankles became so frequent that he was almost continuously incapacitated and unable to pursue his work as a photographer.

Beginning in 1966, the patient was given cryoprecipitate derived from four to five liters of whole blood as a single dose when hemorrhages occurred. This usually prevented further bleeding, but convalescence was still prolonged. Thirteen separate hemarthroses occurred during 1966.

Early in 1967, because of frequent bleeding episodes and prolonged convalescent periods, prophylactic cryoprecipitate treatment was started. The various treatment schedules and the frequency of hemarthrosis are summarized in Table 1. During 1967, while receiving

Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Factor VIII</th>
<th>Approximate Incidence of Hemarthroses Before Therapy</th>
<th>Prophylactic Cryoprecipitate From</th>
<th>Time on Regimen</th>
<th>Hemarthroses on Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>One per month</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>2 months</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Detectable</td>
<td>4 ×/week</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>3 months</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8 L. plasma 4 ×/week</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>24 months</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>One per month</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>4 months</td>
<td>2</td>
</tr>
<tr>
<td>R.E.</td>
<td>Detectable</td>
<td>1.2 L. plasma QOD</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>2 months</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>Two per cent</td>
<td>Five per month</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>2 months</td>
<td>13</td>
</tr>
<tr>
<td>R.B.</td>
<td></td>
<td>1.8 L. plasma 4 ×/week</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>3 months</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>Two per cent</td>
<td>Five per month</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>8 months</td>
<td>1</td>
</tr>
<tr>
<td>B.B.</td>
<td></td>
<td>1.8 L. plasma 4 ×/week</td>
<td>Factor VIII-poor plasma—QOD 1.5 L. plasma 4 ×/week</td>
<td>2 months</td>
<td>2</td>
</tr>
</tbody>
</table>
PROPHYLACTIC TREATMENT OF FACTOR VIII DEFICIENCY

PERCENT NORMAL FACTOR VIII CONCENTRATION

Fig. 1.—Schematic representation of Factor VIII levels in patients II receiving cryoprecipitate derived from 2–4 liters whole blood every 36 hours indicated by arrows. Large dots measured values; small dots based on diffusion and decay rates that are uniform in uncomplicated cases of hemophilia. (11)

cryoprecipitate from 1.2 L. of plasma every other day, he had fewer spontaneous hemarthroses and only one episode of hematuria. Since all of these hemorrhages occurred 36 or more hours after infusion of cryoprecipitate, the dose was increased to cryoprecipitate from 1.8 L. of plasma four times weekly. Because of continued occasional hemorrhages, the dose was further increased to cryoprecipitate from 2.4 liters of plasma four times weekly, and finally to cryoprecipitate from 2.4 liters of plasma given every 36 hours, i.e., five times weekly. On the latter dose schedule the patient’s blood level of Factor VIII varied from 55 per cent immediately following administration of the cryoprecipitate, to approximately 2 per cent just before the next dose (Fig. 1). The patient had only one spontaneous hemarthrosis in seven months on this regimen, and has worked regularly. Spontaneous hemorrhages during a two-month period when Factor VIII-poor plasma was administered were similar to those without therapy.

Case III. (R.B., NIH #07-75-21) and Case IV. (B.B., NIH #07-75-20)

These 12-year-old male identical twins were previously reported as having both classical hemophilia and von Willebrand’s disease. Of the five other siblings, one sister and one brother have von Willebrand’s disease, one brother has classical hemophilia, and two brothers are normal. The patients’ father has von Willebrand’s disease and an uncle and two first cousins of the mother have classical hemophilia.

The diagnosis of both classical hemophilia and von Willebrand’s disease in the twins was indicated by the findings of a Factor VIII level of 2 per cent and an infinite bleeding time despite a normal platelet count. Circulating levels of Factor VIII after cryoprecipitate infusions were equivalent to the dose administered, and decay of Factor VIII began immediately after infusion as in classical hemophilia, e.g., Fig. 1. The twins did not respond to cryoprecipitate with a progressive increase in Factor VIII as do patients with von
Willebrand’s disease. However, their bleeding times remained normal for several hours after cryoprecipitate.

Hemorrhagic manifestations in both included hematoma formation, easy bruising, hematuria, epistaxes and prolonged bleeding from cuts and loose teeth. Hemarthroses were particularly frequent and severe. By the age of 12, R.B. had destructive arthritis of both knees and right shoulder, and B.B. had similar arthritis of both ankles. Observations on the twins with and without therapy are presented in Table 1.

DISCUSSION

Although Factor VIII levels greater than 25 per cent of normal are required to prevent bleeding after surgery or major trauma, much lower levels prevent spontaneous hemorrhage, for “mild” hemophiliacs with levels of approximately 2 per cent of normal rarely bleed spontaneously. Maintenance of Factor VIII levels above 2 per cent of normal at all times in a severely deficient hemophiliac can be accomplished by various dosage schedules. The most efficient utilization of Factor VIII would require continuous infusion or frequent small doses to maintain therapeutic levels. However, since such schedules were too inconvenient and damaged veins excessively, infrequent large doses of the Factor VIII concentrates currently available proved to be the most practical regimen. The initial phase of rapid decline and subsequent rate of Factor VIII decay (Fig. 1) does not change with multiple infusions, hence the required prophylactic dose remains constant.

The incidence of hemarthrosis provided the best basis for clearly assessing the effects of prophylactic therapy, for other bleeding manifestations such as hematoma formation and bruising were too variable. All four patients had fewer hemarthroses during therapeutic periods (Table 1), as well as a decrease in other forms of bleeding. An improvement in psychologic outlook promoted by regular therapy also occurred in each patient, particularly in the first two, who were able to work more regularly.

The limited supply of Factor VIII concentrates and the enormous expense involved limit the applicability of prophylactic treatment of hemophilia to selected cases. Case I, with a hemophilic pseudotumor, illustrates a special circumstance in which the expense of long-term administration of Factor VIII prophylactically can be justified. This complication, particularly when it involves the ilium as in our patient, is usually difficult to resect and has a poor prognosis. After 24 months of prophylactic cryoprecipitate, our patient’s tumor is smaller and softer, and the bone lesion has not progressed. It remains to be seen, however, whether continued therapy will result in complete resolution. Cases II, III and IV illustrate the use of short-term prophylactic therapy to interrupt cycles of frequent bleeding which required amounts of Factor VIII similar to that used for prophylaxis.

Others have suggested that prophylaxis with cryoprecipitate and other Factor VIII concentrates can be successful in reducing the incidence of spontaneous bleeding in hemophilia. In one study, the “incidence of new hemorrhages was halved” when Factor VIII levels did not fall below 2 per cent on a daily dose of a Factor VIII concentrate. In another report, one unit of cryoprecipitate administered every twelve hours over three months was successful in preventing spontaneous hemorrhage in a severe hemophiliac who had been
hospitalized fifteen times in the preceding six months for bleeding episodes. In a third report, no hemarthroses occurred in a severe hemophiliac treated on a prophylactic regimen weekly for 12 months. It is not clear why this patient had a favorable course as for five of seven days each week his plasma levels of Factor VIII must have been below 1 per cent (Fig. 1), which in our experience is a level too low to protect against spontaneous hemorrhage. In our Case I, maintenance of Factor VIII levels greater than 1 per cent prevented spontaneous hemorrhage, whereas maintenance of levels greater than 2 per cent appeared necessary in Case II. Case I required 43.0 Units of Factor VIII per kilogram of body weight per week, and Case II required 107.0 Units of Factor VIII per kilogram per week, although both patients have severe hemophilia, both lead comparably sedentary lives, and intravascular decay of Factor VIII is the same in both (Fig. 1). Why more Factor VIII is necessary to prevent spontaneous hemorrhage in Case II than in Case I is not clear; perhaps local joint conditions in some patients predispose to hemorrhage and thus necessitate slightly higher circulating levels of Factor VIII for prophylaxis. Case II had no evidence of a Factor VIII inhibitor.

The twins in our study (Cases III and IV) would be classified as “mild hemophiliacs” in terms of a circulating Factor VIII of approximately 2 per cent, but they are unusually severe hemophiliacs in terms of bleeding. One of their brothers with classical hemophilia and the same level of Factor VIII rarely bleeds. The associated abnormality responsible for the prolonged bleeding time may account for their unusually severe symptoms. It is clear from Table 1 that both benefited from cryoprecipitate therapy. This benefit may have been due in part to the temporary correction of the bleeding time abnormality of von Willebrand’s disease as well as the increase in Factor VIII, as patient B.B. may have had some benefit from the Factor VIII-poor plasma.

Few complications have arisen as a result of the massive administration of cryoprecipitate in these four patients. Patient III had mild symptoms and laboratory evidence consistent with serum hepatitis. Patient IV had occasional urticarial reactions, which were readily controlled with antihistamines. None of the patients developed inhibitors.

**Summary**

Two patients with classical hemophilia, and twins with a combination of classical hemophilia and von Willebrand’s disease, were treated prophylactically with cryoprecipitate for periods up to two years. All had significantly fewer spontaneous hemorrhages during therapy. The prophylactic regimen required to prevent spontaneous hemorrhage was different in each case. Progressive enlargement of an inoperable hemophilic pseudotumor was arrested in one. Complications encountered included hepatitis in one case and occasional urticaria in another. Prophylactic treatment appears to be practical and indicated in selected cases.

**REFERENCES**


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