Today's Treatment

Blood and Neoplastic Diseases

Haemophilia and Related Disorders

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Introduction

Haemophilia, Christmas disease, and von Willebrand's disease are the commonest of the hereditary haemorrhagic states and together account for about 90% of these disorders. From the point of view of heredity and clinical manifestations, haemophilia and Christmas disease cannot be distinguished from each other. Both conditions show sex-linked recessive inheritance, affect males, and are transmitted by females who may or may not show some signs of an excessive bleeding tendency. The type of bleeding into the muscles and joints is the same in both conditions.

Nevertheless, the cause of the haemostatic defect in haemophilia is different from that in Christmas disease. Bleeding in haemophilia is due to partial or complete lack of factor VIII (antihaemophilic factor, antihaemophilic globulin, A.H.G.) in the blood, whereas in Christmas disease the deficient factor is factor IX (Christmas factor, plasma thromboplastin component, P.T.C.). Before giving treatment it is essential, therefore, to make sure that the condition has been correctly diagnosed and that specific assays for factors VIII and IX have been carried out. This is especially important now that plasma, which was formerly used for treating both conditions, is being superseded by plasma concentrates of factors VIII or IX for the specific treatment of each disease.

Von Willebrand's disease differs from haemophilia and Christmas disease: in general it is a less severe bleeding disorder; it is inherited as an autosomal dominant condition; and it affects males and females equally.

Clinical Features

The first manifestations of severe haemophilia and Christmas disease (0% factor VIII or IX) appear in early childhood and may take the form of external bruising, bleeding from injury to the tongue or mouth, and painful joint or deep tissue haemorrhages. In addition to being painful, deep tissue haemorrhage may press on nerves and blood vessels of the limbs causing paralysis, ischaemia, muscle contractures, and permanent crippling.

Bleeding occurs characteristically and most frequently into joints. These haemorrhages produce swelling and pain there and unless treated promptly and adequately lead to limb deformity and progressive crippling. Haemarthroses appear sometimes as early as a year of age, more commonly from 3 to 4 years onwards, and affect (in descending order of frequency) the knees, elbows, ankles, shoulders, wrists, and other joints. In addition to the distress and pain caused by recurrent joint bleeding, there is considerable disruption of the patient's life at home, at work, and at school.

In the milder form of these diseases joint haemorrhage is infrequent, usually follows some obvious injury, and rarely results in crippling. Without question, the single most important aspect of the management of haemophilia and Christmas disease is the prompt and effective treatment of haemarthroses and muscle haematomas.

Von Willebrand's disease is characterized by a prolonged bleeding time, a reduced level of factor VIII in the blood, and a tendency for bleeding to occur from superficial cuts and scratches and from the mucous membranes of the mouth, nose, gut, and uterus. The deep tissue haemorrhages so characteristic of haemophilia and Christmas disease are extremely rare.

PRINCIPLES OF REPLACEMENT THERAPY

The haemostatic and coagulation defect in haemophilia and Christmas disease can be corrected by giving the patient intravenous transfusions of material containing factor VIII or factor IX, respectively. Replacement therapy aims to raise the plasma concentration of the missing clotting factor in the patient's blood to a level which will bring about haemostasis and to maintain this level until healing of the injury is well advanced. After transfusion, the half-life of factor VIII in the circulation of a haemophiliac is about 12 hours. The half-life of factor IX in a patient with Christmas disease is about 18 hours.

Treatment of Haemophilia

MATERIAL AVAILABLE

At present the only source of factor VIII available for the management of haemophilia is human or animal blood. Factor VIII is labile on storage and rapidly disappears from normal blood or plasma stored at +4°C. As much as half of the original activity may be lost in 48 hours. Fresh plasma, frozen and stored at −20°C to −70°C, loses factor VIII activity much more slowly.

Whole Blood

Transfusion of whole blood should be used to replace blood loss and not to supply factor VIII.

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Plasma

Fresh plasma or plasma frozen when fresh contains more factor VIII activity per ml than does whole blood and has been found useful for the treatment of those haemorrhages which require factor VIII levels of less than 20% for their control. Only in very special circumstances can plasma be used to raise the plasma factor VIII above 20% of normal. Plasma is still used in some centres for the management of spontaneous bleeding and for bleeding after minor injuries, but it is being used less and less now that various kinds of concentrated factor VIII are becoming more widely available.

Cryoprecipitate

When frozen plasma is allowed to thaw slowly some of the plasma's protein remains undissolved until warmed to 37°C. This cold-insoluble protein (cryoprecipitate or cryoglobulin) is rich in factor VIII and is of great value in the management of haemophilic bleeding. Cryoprecipitate does not contain factor IX and is therefore of no value in the treatment of Christmas disease. In general only 40% of the original factor VIII activity in the plasma is recovered in the cryoprecipitate and sometimes the recovery is much less than this.

In most centres cryoprecipitate is supplied frozen in plastic bags, each bag containing cryoprecipitate prepared from plasma from one blood donation. The amount of factor VIII activity in each bag varies, the average content being about 60 units per bag.* By transfusions of cryoprecipitate the patient's factor VIII concentration can be maintained at a level which will allow major surgery to be carried out safely. Cryoprecipitate may be administered by infusion through a drip set or (in the case of small-volume doses) by injection using a syringe. Cryoprecipitate is the mainstay of factor VIII replacement therapy in Britain since it is easily prepared, clinically effective, and usually available at haemophilia centres as well as some other hospitals. Allergic reactions are probably less than with plasma. The main disadvantages of its use are:

(a) the factor VIII content of each bag may vary widely and is not known before it is given to the patient

(b) reconstitution of the cryoprecipitate in a sterile fashion and without wastage of material is time-consuming

(c) it must be stored frozen at or below −20°C.

Lyophilized Human A.H.G.

Protein concentrates rich in factor VIII may be prepared from human plasma by precipitation in the cold with alcohol or ether or certain amino-acids. In their freeze-dried state these preparations may be stored for more than 1 year at 4°C without significant loss of factor VIII activity and are reconstituted immediately before use by adding an appropriate volume of sterile, pyrogen-free distilled water (water for injection B.P.).

Until recently all of the lyophilized material available in the United Kingdom was prepared at three centres: the Plasma Fractionation Laboratory at the Oxford Haemophilia Centre; the Blood Products Laboratory of the Lister Institute of Preventive Medicine, Elstree; and the Protein Fractionation Centre of the Scottish National Blood Transfusion Association, Edinburgh.

During the past year, two preparations of human A.H.G. have become available commercially in this country. Both preparations, Kryobulin and Hemofil, are clinically effective and have not so far caused any reaction in our patients. Their high potency (about 25 units per ml) enables haemostatically effective doses to be administered intravenously in a small volume.

The advantages of freeze-dried material over cryoprecipitate are:

(a) The factor VIII content of the material is known since it is assayed at various stages of production. It is therefore possible to administer a desired amount of factor VIII with some certainty as to the response.

(b) It can be reconstituted easily and rapidly.

(c) Being freeze-dried, it is stable over long periods, even at 4°C. This is of great importance when considering "home treatment" for minor joint and muscle haemorrhages.

The main disadvantage is that freeze-dried preparations are made from large pools of plasma, 60 litres or more, and this probably increases the risk of transmitting hepatitis. Presumably this risk will be greatly diminished as more sensitive methods are devised for detecting hepatitis B antigen in donor blood.

With the commercial A.H.G. preparations the price of the material is a major restriction on its use. At present both commercial preparations of A.H.G. cost about 10p per unit of factor VIII. This means that a course of treatment lasting 10 to 14 days for major abdominal surgery may cost £2,000 to £3,000.

Animal A.H.G.

Pig and beef A.H.G. are available commercially as freeze-dried preparations. Each ampoule of material is reconstituted for use in 50 ml of pyrogen-free distilled water or saline and contains approximately 800 units of factor VIII activity.

Animal A.H.G. may still be useful for the treatment of some patients who have high-titre antibodies to human factor VIII. In all other circumstances, human preparations should be used.

TREATMENT OF SPECIFIC LESIONS

When faced with a patient who requires factor VIII replacement therapy the doctor must ask himself the following questions:

(1) How much factor VIII is to be given to attain the desired factor VIII level?

(2) What type of material is to be used?

(3) How often is it to be given to maintain a haemostatic level?

(4) How long must it be given to allow healing to take place?

(5) Are any other measures required?

The treatment required to control the most common types of haemorrhage seen in haemophilia is summarized in the table.

Haemarthroses and Haematomata

Early spontaneous haemarthrosis and intramuscular haematoma will be controlled by raising the patient's factor VIII level to

Levels of Factor VIII in the Blood and Doses of Different Materials used for Treatment of Different Lesions in Haemophilia

Lesion	Level of Factor VIII desirable in Patient's Blood immediately after Transfusion (% normal)	Therapeutic Material	Factor VIII Dose †(units per kg)
Spontaneous bleeding. Early haemarthrosis	5-20 (0-5)*	Fresh frozen plasma. Cryoprecipitate	10-15
Dangerous haematomas. Multiple dental extraction	20-40 (5-10)	Human A.H.G. concentrate. Cryoprecipitate	15-30
Major surgery. Serious accidents	80-100 (20-25)	Cryoprecipitate. Animal A.H.G.	55-70

*The figures in brackets are the approximate levels to which the patient's factor VIII level will have fallen 24 hours after transfusion.
†A unit of factor VIII is the amount of factor VIII present in 1 ml of fresh average-normal citrated plasma

*1 unit of factor VIII activity is the amount present in 1 ml of fresh citrated normal plasma (1 part 3.8% citrate to 9 parts of blood).

15% to 20% of normal. This can be achieved by means of a single infusion of cryoprecipitate or lyophilized A.H.G. in a dose of 10 to 15 units of factor VIII per kg body weight. Having received his dose, the patient rests for a short period of up to an hour or two and then may return to school or work. If the bleeding does not resolve completely after a single dose, a second dose should be given the following day.

Severe traumatic haemarthrosis and muscle haematoma may require factor VIII levels of over 30%. Treatment with cryoprecipitate or lyophilized A.H.G. in a dosage of 15 to 30 units of factor VIII per kg body weight should be given daily for two to four days. In addition, it is often necessary to immobilize the limb in a padded plaster-of-paris splint until pain has subsided. Further doses of factor VIII should be given on the first day or two of active mobilization of the joint.

Major Surgery

Major surgery such as pyloroplasty and vagotomy, or resection of carcinoma, requires that the patient's factor VIII level be maintained above 40% for the first six to 10 days after surgery. This can be achieved by giving a preoperative dose of factor VIII of 60 units/kg followed by 12-hourly infusions of factor VIII (30 units per kg) for the next six to 10 days, and once daily thereafter until wound healing is well advanced. The total duration of replacement therapy is usually 10 to 21 days, but may be longer if wound healing is complicated by infection or haematoma formation.

Dental Extraction

Dental extraction can be carried out with minimal factor VIII replacement therapy provided an antifibrolytic agent such as epsilon-amino caproic acid (Epsikapron, EACA) or tranexamic acid (Cyclokapron) is given before and during the postoperative period.

The regimen at Oxford for patients undergoing dental extraction is as follows:

On the morning of operation the patient is given a dose of cryoprecipitate or lyophilized human A.H.G. sufficient to raise his factor VIII level to 50% of average normal (30 to 40 units of factor VIII, per kg body weight). At the same time he is given E.A.C.A. intravenously, in a dosage of 0.1g per kg. Thereafter he is given E.A.C.A. 0.1g per kg 6-hourly by mouth for seven to 10 days. The patient is also given oral penicillin in a dosage of 250 mg 6-hourly for seven to 10 days.

No further doses of factor VIII are given unless the patient bleeds. Tranexamic acid may be used instead of E.A.C.A. A dose of 1g is given intravenously before operation, followed by a dose of 1g 6-hourly for the next seven to 10 days. Children receive half this dose.

Treatment of Christmas Disease

In general the principles of replacement therapy in Christmas disease are the same as for haemophilia. Roughly the same levels of factor IX as of factor VIII are required for haemostasis in the different lesions already described in the section on haemophilia. The half-life of transfused factor IX in a patient with Christmas disease is approximately 18 hours. Unfortunately this apparent advantage over factor VIII is offset by a poorer recovery of factor IX in the patient's blood after transfusion. This means that more factor IX units are required to attain a given level of factor IX in the patient than factor VIII units to produce the same level in a haemophiliac.

Plasma collected and frozen fresh for the treatment of haemophilia is also suitable for treating Christmas disease. Plasma given in a dose of 15 to 20 ml per kg body weight will raise the patient's factor IX level by 5% to 10%. This may be adequate for the control of minor haemorrhage but for more severe bleeding, especially after injury or surgery, it is necessary to use a factor IX concentrate to attain haemostasis.

Lyophilized protein fractions rich in factor IX (and also factor II and X or factors II, VII and X) are made at the Plasma Fractionation Laboratory at the Oxford Haemophilia Centre and at the Protein Fractionation Centre of the Scottish National Blood Transfusion Association, Edinburgh. These preparations have been shown to be clinically effective in the management of Christmas disease and in our experience cause no side effects.

For a mild haemarthrosis a single dose of factor IX concentrate (10 to 20 units of factor IX per kg body weight) will usually control haemorrhage. For more severe haemarthroses and intramuscular haemorrhages, a large dose (40 to 50 units per kg) on two or three successive days may be required to maintain haemostasis.

After major surgery it is generally advisable to maintain the patient's factor IX level above 30% of average normal. This can be achieved by giving factor IX in a dosage of 50 units of factor IX per kg 12-hourly after a preoperative dose of 80 units per kg. As in haemophilia, replacement therapy should be continued until the wound is consolidated.

Treatment of Von Willebrand's Disease

Post-traumatic bleeding in von Willebrand's disease can generally be controlled if the level of factor VIII in the patient's blood is raised by transfusion therapy and if the bleeding site can be obliterated, packed, or sutured. After transfusion of plasma or A.H.G., the level of factor VIII in the plasma of a patient with von Willebrand's disease remains raised much longer than in the haemophiliac. Because of this prolonged response, it is easy to maintain the patient's factor VIII concentration at a haemostatic level. Treatment with fresh frozen plasma (800 to 1,000 ml daily) is probably sufficient for even major surgical procedures. In severely affected patients, however, it is wise to treat with lyophilized human A.H.G. or cryoprecipitate. The level of factor VIII arrived at should be about the same as for a haemophiliac undergoing the same operation.

Any Questions?

We publish below a selection of questions and answers of general interest

Mechanism of Finger Clubbing

By what mechanism is clubbing of the fingers produced?

Finger clubbing occurs in many conditions including bronchial carcinoma, bronchiectasis and lung abscess, fibrosing alveolitis and other types of diffuse lung fibrosis, congenital cyanotic heart disease, bacterial endocarditis, and cirrhosis of liver. The conditions in this far from exhaustive list appear at first to have no common factor. In most of them, however, some blood is shunted past the pulmonary alveoli so that not *all* the blood from the right side