PROPHYLACTIC ADMINISTRATION OF CRYOPRECIPITATE IN HAEMOPHILIA

A Controlled Trial

It has been suggested that the frequency of occurrence of haemarthroses in severely affected haemophiliacs can be reduced by the routine administration of factor-VIII concentrates at intervals of 2-4 weeks (1). The aim of prophylaxis should be to reduce spontaneous bleeding episodes without greatly increasing the total amount of therapeutic materials (containing factor VIII) required. Controlled trials have not, however, been carried out to determine whether this aim can be achieved.

If prophylaxis is to have any chance of benefitting an individual patient, the frequency of spontaneous haemorrhage experienced by that patient in the past must approach the contemplated frequency of routine administration of factor VIII. Thus only clinically severely affected patients would be likely to benefit from prophylaxis.

The effects of prophylactic administration of factor-VIII concentrates may be complex. For example a patient may gain sufficient assurance from such treatment to ignore symptoms which would ordinarily cause him to consult his physician. Conversely he may be prompted to exert himself more strenuously than he might otherwise and thereby provoke a bleeding episode. The effects of psychological influences on bleeding in haemophilia have been stressed (2). It would be desirable to control these sources of potential bias by designing a trial with two specific requirements. First, the variation among patients might be controlled by a "switchback design", whereby each patient serves as his own control. Secondly, the individual

variation of a single patient between control and treatment periods might be controlled by employment of a double-blind requirement. This requirement would be feasible and would entail only minimal inconvenience to the patients.

The prospect of administering a placebo to haemophiliacs, even when there is no evidence that prophylactic administration of factor VIII has any therapeutic value, may not be acceptable to some physicians. An alternative to placebo administration is the comparison of high-dose and low-dose regimes. Thereby the potential risk of haemorrhage at venepuncture sites in haemophiliacs not 'covered' with factor VIII would be avoided.

An ideal location for carrying out a clinical trial to evaluate prophylaxis would be a centre where a relatively large number of severely affected haemophiliacs are closely observed daily; where the 'baseline' bleeding habits of the patients are known; and where personnel and facilities exist for separating clinical management from trial administration. Such a location is the Lord Mayor Treloar College.

I. Eligibility Criteria

All classical haemophiliacs who fulfil the following eligibility criteria will be admitted to the trial.

1. Age, 7 or over.
2. Sex, male.
3. Factor-VIII level, 1% or less.

4. The average number of bleeding episodes* (including haemarthroses, haematomata, epistaxes and haematuria) during the two school terms prior to admission to the trial must exceed 7 per 100 days.
5. Patients with factor-VIII inhibitors will be excluded.
6. Patients in whom elective surgery is anticipated during the trial period will be excluded or their admission to the trial delayed.
7. Patients participating in studies with conflicting requirements will by necessity be excluded.
8. All patients must give their informed consent as defined below, prior to the final determination of eligibility.

II. Baseline Clinical Information Required

Historical information and physical findings as detailed in the data forms will be recorded before determination of patient eligibility.

III. Baseline Laboratory Studies Required

1. Two-stage factor-VIII assay (3).
2. Factor-VIII inhibitor assay (4).

IV. Trial Design

The trial for an individual patient will consist of four preferably sequential school terms. During

---

*Any discrete episode of joint, muscle, subcutaneous, genitourinary or nasal haemorrhage, whether or not preceded by trauma, which in the opinion of the investigator was sufficiently well-documented and serious enough to have been treated with factor-VIII containing material, regardless of whether it was in fact treated.

two of these terms the patient will receive once weekly infusions (see below) of high-dose cryoprecipitate, and during the other two terms, once weekly infusions of low-dose cryoprecipitate. The designation of these terms as high-dose or low-dose periods will be made on a random basis.

Whenever possible the trial will be completed for an individual patient within four consecutive school terms. However it may be necessary under special circumstances to delay a treatment period for an interval not to exceed one school term. The total trial period shall in no instance exceed six school terms.

V. Division of Responsibility

To implement the double-blind requirement it will be necessary to divide responsibility for clinical management and trial administration among several individuals, as follows:

1. The physician responsible for clinical management will be 'blind' to the treatment assignment. He will be responsible for obtaining informed consent, determining patient eligibility, completing data forms, and deciding what treatment is required for bleeding episodes when they occur.
2. The physician responsible for trial administration will receive data forms indicating eligibility of patients for the trial. He will assign patients

to a treatment schedule by reference to a table of random numbers and inform the physician responsible for therapeutic infusions each term which patients are to receive high-dose and which low-dose prophylactic regimes.

3. The physician responsible for therapeutic infusions will administer cryoprecipitate to patients. He will give high-dose or low-dose prophylactic infusions once weekly according to treatment assignments. He will also give therapeutic infusions of cryoprecipitate when required for a bleeding episode, but since he is not 'blind' to the treatment assignment, he must receive instructions about this from the physician responsible for clinical management.

VI. Informed Consent

After tentative determination of a patient's eligibility, the trial will be explained fully to the patient and the patient's parents or guardian. The following points will be made clear:

1. During the entire trial each patient will receive an infusion once weekly of either high-dose or low-dose cryoprecipitate.
2. The patient will not be told to which treatment he is assigned.
3. It must be understood that the only safe assumption for the patient to make is that he is assigned to the low-dose group. He should act accordingly by not taking undue risks and by promptly reporting symptoms suggesting haemorrhage as usual.

4. All patients will receive best available treatment as usual for bleeding episodes when they occur. Symptoms should be reported promptly as usual.
5. Patients must agree to participate in the trial for a full four terms once accepted and should understand that prophylactic administration of factor VIII will not be available during the trial to patients who opt not to participate.

VII. Determination of Patient Eligibility

A patient will be considered eligible for admission to the trial when the data forms entitled "Determination of Patient Eligibility" have been completed by the physician responsible for clinical management and received by the physician responsible for trial administration.

VIII. Randomization Procedure and Treatment Assignment

Having received the data forms referred to above, the physician responsible for trial administration will provide the physician responsible for therapeutic infusions with a schedule for assigning the patient to treatment with high- or low-dose cryoprecipitate during each of the four treatment periods.

IX. Prophylactic Administration of Cryoprecipitate

Once weekly the patient will receive an infusion of high- or low-dose cryoprecipitate depending on which treatment period is current. Cryoprecipitate will be

given in an amount calculated to produce a plasma factor-VIII level of 25% average normal when the patient is receiving the high-dose regime, 2-5% when on the low-dose regime. The following table will be used to determine the weekly dose according to the weight of the patient.

Weight of Patient (Kg)	Amount of Cryoprecipitate Given* (Number of Donors)	
	High-Dose	Low-Dose
< 15	2	0.5
15-25	3	0.5
26-32	4	0.5
33-39	5	0.5
40-46	6	0.5
47-54	7	0.5
55-61	8	0.5
62-68	9	1
69-75	10	1
> 76	11	1

An attempt will be made to maintain the total volume of the infusion given to an individual patient the same throughout the trial, so that the patient will not be given an indication whether he is receiving high- or low-dose cryoprecipitate. The infusion bottle and tubing will be concealed from the patient's view for the same reason. Needles used for prophylactic infusions will have an outside diameter no greater than 21 gauge. Precautions will be taken to maintain firm pressure on the infusion site until haemostasis is assured.

---

*The amount of cryoprecipitate administered is given as that amount of cryoprecipitate obtained from a number of individual single unit blood donations.

X. Treatment for Bleeding Episodes

Treatment with fresh frozen plasma or factor-VIII concentrates will be given as required for bleeding episodes in the usual manner at the treatment centre. In all instances requiring replacement therapy, the patient will be evaluated by the physician responsible for clinical management and information concerning the bleeding episode and treatment required will be recorded as detailed in the data forms.

XI. Follow-up Clinical Information

Complete information will be recorded as detailed in the data forms for each of the four treatment periods. At the end of each treatment period the data forms relating to that period will be sent to the physician responsible for trial administration.

XII. Follow-up Laboratory Information

At the beginning of each trial period, a factor-VIII inhibitor assay (4), will be performed. On at least three occasions during each trial period, the high- or low-dose cryoprecipitate and pre-infusion and post-infusion plasma factor-VIII levels will be assayed.

XIII. Special Problems

A. Bleeding episode requiring treatment within 24 hours prior to a prophylactic dose.

It is anticipated that upon occasion a bleeding episode will occur shortly before a scheduled prophylactic dose of cryoprecipitate. If a bleeding episode occurs which requires treatment within 24 hours prior to the next scheduled prophylactic dose, the administration of that prophylactic dose will be delayed until 24-48 hours after the last dose of replacement therapy for the bleeding episode in question. Thereafter the schedule of administration of prophylactic doses may be adjusted to the convenience of the patient.

B. Development of factor-VIII inhibitors.

If at any time during the trial, a patient develops inhibitors to factor VIII, this will be noted on the data forms which will be sent to the physician responsible for trial administration, and the patient will be withdrawn from further participation in the trial.

C. Patients withdrawn from the trial.

Extreme efforts must be made to assure that, once admitted to the trial, a patient fulfil all its requirements. For a variety of reasons (e.g., development of factor-VIII inhibitors, serious intervening illness, necessity to move out of the country, lack of patient cooperation, etc.) it may be necessary to withdraw patients from further participation in the trial. However, it must be realized that

at the moment of treatment assignment, patients are for purposes of data analysis irrevocably admitted to the trial. All available information must be sent to the Physician responsible for trial administration in the event withdrawal is unavoidable.

REFERENCES

1. NILSSON, I.M., BLOMBACK, M. & AHLBERG, A. (1970) Our experience in Sweden with prophylaxis on haemophilia. Bibliotheca Haematologica, 34, 111.
2. LUCAS, O.N. (1970) Hypnosis and stress in hemophilia. Bibliotheca Haematologica, 34, 73.
3. BIGGS, R. & MACFARLANE, R.G. (1966) Treatment of Haemophilia and Other Coagulation Disorders. Blackwell Scientific Publications, Oxford.
4. BIGGS, R. & BIDWELL, E. (1959) A method for the study of antihaemophilic globulin inhibitors with reference to six cases. British Journal of Haematology, 5, 379.