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Prophylaxis in Haemophilia: A Double-blind Controlled Trial

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Summary. A double-blind controlled trial of prophylactic factor VIII therapy has been carried out on nine severe haemophiliacs at the Lord Mayor Treloar College. Infusions were given once weekly and calculated to give a post-infusion plasma concentration of at least 0.25 I.U./ml of factor VIII. This regime reduced the overall bleeding frequency by 15%. The bleeding frequency in the first 3 days post-infusion was reduced by 66%. A moderate overall reduction in morbidity was also achieved. It is calculated that to reduce the incidence of bleeding in severe haemophiliacs by 15% would require a 73% increased usage of therapeutic materials. More than twice this amount of material is likely to be needed to reduce the bleeding frequency of the same group by 66%.

The quality of life in a severe haemophiliac is limited by the frequency with which he bleeds. Current therapy is aimed at treating established bleeding episodes, although several attempts at prevention of bleeding have now been documented (Bellingham *et al*, 1967; Robinson *et al*, 1967; Shaubrom & Thelin, 1969; Nilsson *et al*, 1970; Kasper *et al*, 1970; Hirschman *et al*, 1970; Van Creveld, 1971; Ramsay & Parker, 1973).

Widely different regimens have been instituted and marked variations in the time between prophylactic doses and the amount of factor VIII in a given dose have been tried. The results have not been consistent. Nilsson *et al* (1970) used doses of 300 I.U. every 2–4 weeks and claimed a reduction in frequency of bleeding episodes. In contrast Robinson *et al* (1967) gave one unit of cryoprecipitate, about 70 I.U. of factor VIII, twice daily and reduced a bleeding frequency of eight in 3 months to nil over a similar subsequent period, but this was in only one patient. Ramsay & Parker (1973) gave six units of cryoprecipitate weekly to two patients and were not able to demonstrate an overall reduction in bleeding frequency.

No controlled trial of prophylactic treatment has as yet been reported. Several sources of potential bias require elimination in an attempt to evaluate such a regimen, e.g. a patient may gain sufficient assurance to ignore symptoms which would ordinarily cause him to seek treatment and advice. He might be prompted to exert himself more strenuously than otherwise and thereby provoke a bleeding episode. The effects of psychological influences on bleeding have been stressed (Lucas, 1970). Furthermore, observer bias cannot be eliminated if diagnosis of a marginal bleeding episode is left to an observer who wishes to show that prophylaxis is beneficial and who knows that the patient is on a prophylactic regimen. His management of a patient may also be affected if he knows that a dose of therapeutic material will shortly follow the presentation of an equivocal bleed, as he may be tempted not to treat

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that bleed routinely. These sources of potential bias can be controlled by designing a trial with three specific requirements. Firstly, the variation among patients is eliminated by a cross-over design whereby each patient serves as his own model for comparison. Secondly, the individual patient should not know whether he is or is not receiving prophylaxis: this may be achieved by using a placebo or an extremely low dose of factor VIII and employing a double-blind method. Thirdly, the clinician responsible for the diagnosis of a bleeding episode should not know whether the patient is receiving factor VIII or a placebo. The Treloar Haemophilia Centre has a relatively large number of severely affected haemophiliacs. The 'baseline' bleeding habits are known and carefully documented (Rainsford & Hall, 1973). It includes the Lord Mayor Treloar College, the Coagulation Laboratory at the Lord Mayor Treloar Hospital at Alton, which is 5 miles from the College, and the Haemophilia Ward at the Hospital. The Lord Mayor Treloar College is a school for crippled children at Froyle, near Alton; 50 of the pupils are haemophiliacs. Personnel facilities exist for separating clinical management and trial administration and it is therefore an ideal location for the carrying out of such a trial.

MATERIALS AND METHODS

Clinical management of the boys on the trial was carried out at various times by a Research Fellow (S.G.R.), a GP Clinical Assistant, a College Medical Officer and a Senior House Officer (P.J.K.). These were at all times blind to the particular trial dosage of the different boys, although they were aware that any given boy was on the trial. Diagnosis of a bleeding episode requiring treatment was made at the College, routine treatment was given at either the College or the Haemophilia Unit at the hospital and prophylactic treatment was given at the hospital. The majority of these infusions were given by one of us (P.T.) and none was given by the doctors designated above.

Eligibility Criteria

Only classical haemophiliacs over 7 years of age and with a factor VIII concentration of less than 0.01 I.U./ml were selected. Before admission to the trial each boy was observed for at least two school terms and had to have a baseline bleeding frequency of at least seven bleeding episodes per 100 d during those terms. Patients with inhibitors to factor VIII were excluded.

A bleeding episode was defined as any spontaneous discrete episode of joint, muscle, subcutaneous, genito-urinary or nasal haemorrhage which required treatment with factor VIII containing material. Only patients who were potentially available for at least four school terms were considered.

The nature of the trial was fully explained to the eligible boys and their parents or guardians were asked to give their consent; if this was obtained the boy was admitted to the trial.

Trial Design

An attempt was made to give once-weekly infusions of either a factor VIII concentrate calculated to raise the boys' factor VIII level to at least 0.25 I.U./ml or a concentrate calculated to raise the level of factor VIII by not more than 0.01 I.U./ml.

The concentrates were made in the Blood Products Laboratory of the Lister Institute for Preventive Medicine and they were as nearly indistinguishable visually as possible. As an

To avoid wastage and for convenience this was made up to the nearest 200 I.U. As the boy's weight increased during this trial, the dosage was recalculated and adjusted as necessary.

Prophylactic material (low dose) consisted, after reconstitution of a full bottle to 50 ml, of 2% human albumin plus the above concentrate to give an estimated 10 I.U. of factor VIII per bottle. The same volume of material was administered as during high-dose periods.

Patients

Patient 1. Born GRO-A 1960, weight 43 kg on admission to trial. Had frequent bleeds involving knees, elbows, ankles and sometimes the muscles on both upper and lower limbs. The right knee was most frequently involved and was the only joint showing any signs of permanent disablement. Radiological appearances typical of haemophilia seen in both knee joints and elbow joints.

Patient 2. Born GRO-A 1958, weight 37 kg on admission to trial. Two maternal uncles suffered from this disease. Bled into most joints and muscles of all limbs. Radiological changes typical of haemophilia seen in elbows, knees and ankles.

Patient 3. Born GRO-A 1961, weight 33 kg on admission to trial. No family history. Both elbow and knee joints showed some permanent disablement. Radiological changes typical of haemophilia seen in knees, ankles and elbows. He had never presented with a muscle bleed.

Patient 4. Born GRO-A 1958, weight 60 kg on admission to trial. One brother suffered from severe haemophilia with a factor VIII inhibitor. His maternal grandfather had haemophilia and died from intracranial haemorrhage. Had suffered from numerous bleeds involving elbows, knees, ankles and sometimes the muscles of both upper and lower limbs. Radiological changes typical of haemophilia could be seen in the elbow, knee and ankle joints. Clinically these joints showed some degree of permanent disablement.

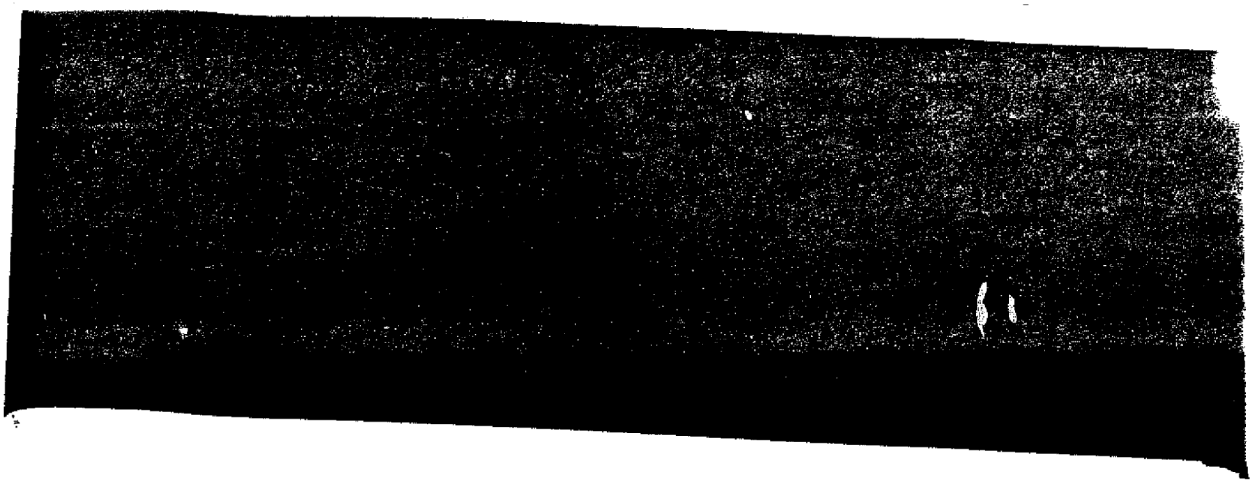
Patient 5. Born GRO-A 1958, weight 30 kg on admission to trial. No family history. Frequent bleeds had affected his knees, elbows, shoulders, wrists and ankles. He had never suffered from a muscle bleed. Both knee joints showed some degree of permanent disablement. Radiological appearances typical of haemophilia seen in most joints.

Patient 6. Born GRO-A 1958, weight 57 kg on admission to trial. One brother had severe haemophilia. Most haemorrhages had involved knee joints and elbow joints. He occasionally suffered from muscle bleeds. Radiological appearances typical of haemophilia seen in elbow and knee joints.

Patient 7. Born GRO-A 1958, weight 50 kg on admission to trial. No family history. Had suffered from numerous bleeds involving joints of elbows, knees and right shoulder. Did not suffer from muscle bleeds. The right elbow and both knees showed some degree of permanent disablement. Radiological appearances typical of haemophilia seen in the joints of both knees and the right elbow.

Patient 8. Born GRO-A 1961, weight 33 kg on admission to trial. No family history. Had numerous bleeds into his knees and ankles. His left knee was the worst affected and was the only joint which showed some degree of permanent disablement with wasting of the quadriceps. He had bled into the muscles of his limbs. Both knee joints showed radiological changes typical of haemophilia.

Patient 9. Born GRO-A 1962, weight 30 kg on admission to trial. No family history. Had numerous bleeds into both elbows and both knee joints. Both elbows and the right knee joint



showed some degree of permanent disablement. The right elbow joint was very distorted in outline due to the presence of a number of haemophilic cysts. Radiological changes typical of haemophilia seen in both elbows, right knee and left ankle. He also suffered from occasional bleeds involving the muscles of his limbs.

RESULTS

Nine boys were studied for a total of 27 boy-school terms. A 'boy-school term' is defined as the whole or any part of any school term during which an individual boy was under observation; the whole study took place during five school terms. The boys' bleeding frequencies with high-dose material were studied during 14 boy-school terms and with low-dose material during 13 boy-school terms. Ninety-seven infusions of high-dose and 95 of low-dose material were given.

Overall Bleeding Frequencies

The findings during the two pre-trial and trial terms are shown in Table I. There is a small

TABLE I. Overall bleeding frequencies

Case	*Pre-trial terms*			*Low-dose terms*			*High-dose terms*		
	No. of bleeds	*Days under observation*	*Bleeds per 100 d*	*No. of bleeds*	*Days under observation*	*Bleeds per 100 d*	*No. of bleeds*	*Days under observation*	*Bleeds per 100 d*
1	17	169	10.0	19	143	13.3	15	124	12.1
2	27	169	16.0	6	27	22.2	24	125	19.2
3	31	169	18.3	22	147	15.0	10	94	10.6
4	17	169	10.0	11	79	13.9	5	60	8.3
5	27	169	16.0	16	79	20.3	9	52	17.3
6	12	148	8.1	8	139	5.8	6	151	4.0
7	27	176	15.3	11	64	17.2	7	56	12.5
8	22	168	12.3	6	37	16.2	8	72	11.1
9	25	168	14.1	8	72	11.1	6	45	13.3
Mean	22.8	167.2	13.6	11.9	87.4	13.6	10.0	86.6	11.6

but statistically significant reduction in the number of bleeds per 100 d amongst those on high dosage ($P<0.05$). The mean difference for all boys is a reflection of a fairly consistent difference for each individual child; eight out of the nine boys had a lower proportion of bleeds when on high-dose compared with low-dose prophylaxis.

Distribution of First Bleeds on Individual Days

Table II shows the number of bleeds which occurred on each individual day following a planned infusion. Only the first bleeds following each infusion have been recorded. It is assumed that any subsequent bleed before the next prophylactic infusion was no longer related to the original infusion.

In order to obtain comparable data from the high- and low-dose groups we have expressed

TABLE II. Distribution of first* bleeds on individual days following high- or low-dose infusions

Patient	High-dose infusion							Low-dose infusion						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	0	1	2	1	0	1	2	0	6	1	0	2	1	2
2	0	0	1	1	1	1	2	0	6	3	1	2	1	2
3	0	0	0	1	2	0	0	0	1	2	0	1	0	1
4	0	1	2	5	4	3	0	0	0	1	2	0	0	0
5	0	0	0	0	2	0	1	0	4	0	1	0	0	1
6	0	1	0	0	2	2	2	1	1	2	0	2	1	0
7	1	1	0	0	1	1	1	1	2	3	1	0	0	0
8	0	0	1	0	1	3	2	1	0	1	1	0	1	1
9	0	0	0	1	0	1	3	0	1	1	2	0	1	1
Totals	1	4	6	9	13	12	13	3	21	14	8	7	5	8

* Only the first bleed following an infusion has been recorded; any subsequent bleed occurring before the next 'prophylactic' infusion is no longer related to the previous 'prophylactic' dose.

the number of bleeds on each day as a percentage of possible bleeds on that day (Table III). Ninety-five infusions of low-dose material were given during the trial thus creating a potential 95 first bleeds. Of the 95 possible bleeds on day 1 only three took place, which is expressed as a percentage of 95. On day 2 there were 92 possible first bleeds or days at risk. This is because it was no longer possible to have first bleeds related to the three infusions which were followed by bleeds on day 1. Twenty-one bleeds occurred on day 2 which is expressed as a percentage of 92. On day 3 there were only 71 possible bleeds because by now 24 of the original 95 bleeds had been followed by first bleeds. The 14 bleeds which occurred on day 3 are thus expressed as a percentage of 71 and so on.

The difference in bleeding frequency following high and low doses is significant on day 2

TABLE III. First bleeds on individual days expressed as a percentage of possible bleeds

Day	High-dose infusion			Low-dose infusion			Significance of difference (P value)
	Bleeds recorded	Possible bleeds	Percentage bleeds	Bleeds recorded	Possible bleeds	Percentage bleeds	
1	1	97	3.0*	3	95	9.5*	0.06
2	4	96	4.2	21	92	22.8	<0.001
3	6	92	6.5	14	71	19.7	0.02
4	9	86	10.5	8	57	14.0	0.57
5	13	77	16.9	7	49	14.2	0.69
6	12	64	18.8	5	42	11.9	0.32
7	22	52	23.0†	10	37	16.2†	0.42

* Adjusted from ½ to 1 day.
† Adjusted from 1½ to 1 day.

and day 3 and approaches the 5% level of significance on day 1, even though it is only based on bleeds after 16.00 hours. The daily mean bleeding frequency following the low-dose infusion is 15.5 and the frequency of 22.8 on day 2 is significantly higher than this ($P<0.05$). However, if the bleeds during the 8 h of day 1 are added to those in the 24 h of day 2 and the appropriate adjustments made, then the difference in bleeding frequency is no longer significant. These results have been presented in Fig 1, which indicates visually the major difference in the bleeding rate on the first days after the infusion.

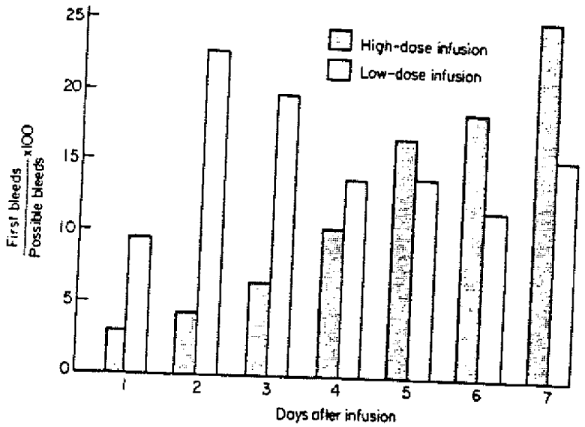


FIG 1. First bleeds on individual days expressed as a percentage of possible bleeds.

Time to First Bleed

The interval times from administration of high- or low-dose material to the first bleeds thereafter have been pooled and compared. When an infusion was followed by a clear week, all subsequent infusions until the next bleeding episode were ignored, for example, if an infusion was followed by 2 clear weeks and the next bleed occurred on day 2 of the subsequent cycle, it was recorded as one infusion, with an interval time of 16 d to the first bleed thereafter. The mean interval times were significantly longer ($P<0.05$) in the boys on high dose (8.3 days) than in those on low dose prophylaxis (6.6 days).

Clear Weeks

Twenty-nine out of 95 administrations of low-dose material (30.5%) were followed by a clear week. Thirty-nine out of 97 high doses (40.2%) were followed by a clear week. The difference is not significant ($P = 0.16$).

Morbidity

The time spent either in the college sick bay or at the hospital during high- and low-dose regimens was recorded. More than 3 h under medical care was noted as 1 d. The total figures are shown in Table IV. The children on high-dose spent significantly less time confined to bed ($P<0.05$).

TABLE IV. Morbidity

Pre-trial terms			*Low-dose infusion*			*High-dose infusion*		
Days under medical care	*Days under observation*	*Morbidity per 100 d*	*Days under medical care*	*Days under observation*	*Morbidity per 100 d*	*Days under medical care*	*Days under observation*	*Morbidity per 100 d*
310	1505	20.6	171	787	21.7	130	779	16.7

Development of Inhibitors

No case of an inhibitor to factor VIII developed during the trial.

Hepatitis Associated Antigen

No case of hepatitis associated antigen developed during the trial, although one boy (patient 2) developed antigen negative hepatitis 23 d after entering the trial. He was withdrawn for the remainder of that term.

Factor VIII Assay

Twenty-three random assays on blood taken 30 min after the infusion of low-dose material were undertaken. All but two of these showed less than 0.05 I.U./ml of factor VII to be present, the two aberrant assays being 0.05 and 0.06 I.U./ml. Twenty-three assays were performed at random on samples taken 30 min after high-dose material. All but three of these were over 0.2 I.U./ml (mean 0.26 I.U./ml). Random assays were carried out on each batch of materials at the Lister Institute and each confirmed the predicted strength.

DISCUSSION

The raising of the factor VIII level in severe haemophiliacs to at least 0.2 I.U./ml once weekly has been shown to reduce the overall bleeding frequency from 13.6 to 11.6 bleeds per 100 d. This small but significant reduction in bleeds amongst the high-dose group is due to a modest reduction in bleeds amongst eight out of the nine boys on the high-dose prophylaxis. A 15% reduction in the overall bleeding frequency of severe haemophiliacs can therefore be achieved by weekly prophylaxis. We had deliberately picked the dose of factor VIII containing materials which we would normally use for spontaneous, uncomplicated, bleeds. In our experience (Rainsford & Hall, 1973) each spontaneous bleed needs an average of 1.2 doses of therapeutic material. The overall bleeding frequency of 13.6 bleeds per 100 d therefore needs 16.3 doses of therapeutic material per 100 d. Weekly prophylaxis reduces the bleeding frequency to 11.6 bleeds per 100 d. If 1.2 doses of therapeutic material are used to treat each bleed then 13.9 doses per 100 d will be needed to treat 11.6 bleeds per 100 d. In addition, 14.3 prophylactic doses would be given in 100 d (one prophylactic dose each week for 100 d), making a total of 28.2 doses of therapeutic material on 100 d. Thus a 73% increase in therapeutic materials is required to reduce by 15% the frequency of bleeding in a group of severe haemophiliacs. This may well be an underestimate of the factor VIII needed as the boys at

the Lord Mayor Treloar College are probably seen earlier in their bleeds than most other haemophiliacs. Prompt treatment of bleeding could reasonably be expected to reduce the number of occasions when more than one infusion is needed for a bleed.

The reduction in bleeds occurs predominantly in the first 3 d after infusion. The difference in the bleeding frequencies on high- and low-dose prophylaxis is statistically significant on the second and third days and nearly so on the first day. It is difficult to explain the increased bleeding frequency on day 2 following the low dose. The possibility that the boys became over confident, believing themselves to be protected, cannot be excluded, although they denied this. It should also be stressed that these were a group of boys who bled frequently. We insisted that at least 24 h had to elapse from the last therapeutic infusion before a prophylactic dose and did not give any prophylaxis during the weekends. This meant that the second day after a low-dose infusion was often the fourth or fifth day since the last bleed and many of the boys on our trial would expect a fresh bleed at about that time. Whatever the reason, this increased bleeding frequency following the low-dose infusion must cast some doubt on the validity of comparing the high and low doses and is one example of the difficulties associated with the use of a placebo in this trial.

The mean bleeding frequency during the first 3 d after the high-dose infusions was approximately two-fifths of the mean bleeding frequency over all 7 d following a high dose. It is about one-third of the mean bleeding frequency in the 7 d following a low dose. Taking the most optimistic view, it might be predicted that a prophylactic dose of the order used in our trial, given every third day, would reduce the bleeding frequency in severe haemophiliacs by two-thirds. The average bleeding frequency of the boys in our trial was 13.6 bleeds per 100 d. If these were reduced by two-thirds then 4.5 bleeds would occur in 100 d. Assuming 1.2 doses of therapeutic material was used on average per bleed then 5.4 doses of therapeutic material would be needed to treat these bleeds in 100 d but in addition 33.3 prophylactic doses would be given in 100 d, making a total of 38.7 doses of therapeutic material. This is nearly 2.5 times more material than the 16.3 doses needed to treat the average of 13.6 bleeds per 100 d occurring in the boys on the trial. It thus appears that a substantial reduction in bleeding frequency by prophylaxis is likely to require a great increase in the supply of therapeutic materials. In view of the implications for the limited financial and human resources needed to service such a commitment, it is important that further trials are undertaken to establish the lowest dose which might be beneficial and what the optimum frequency should be.

We found many problems in this trial. Some bleeds were bound to occur shortly after infusions of low-dose material and sooner or later a crop of bleeds will occur. On one occasion four boys were together in the sick bay within 24 h of a low-dose infusion. They concluded that the material was the cause for their bleeding and it was difficult to persuade them to remain in the trial. Two, in fact, dropped out soon after this episode. The giving of a dose interferes with a boy's leisure and schooling and when inert material is being given this may not now be easily justified. In our view, future trials should compare only probably effective prophylactic regimens, and should not include placebo doses.

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