bjh review

Dose and response in haemophilia – optimization of factor replacement therapy

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Summary

The mainstay of the management of haemophilia is the replacement of clotting factors, using clotting factor concentrates (CFC) in a way that prevents bleeding and its complications. Beginning with small doses, as whole blood and plasma over 50 years ago, highly purified CFCs are now administered frequently in large doses to effectively treat this condition so that even people with severe haemophilia can lead near normal lives. However, with such regimens, compliance and expense have both become significant issues. The question therefore is whether the current models of clotting factor replacement are optimal. This article reviews the literature on the dose–response relationship in haemophilia, with particular reference to management of musculoskeletal bleeding and surgical haemostasis. Current practices are based on uncontrolled observational data. Less intensive protocols could achieve similar outcomes. Large multi-centre prospective studies are needed to provide comparative data on unresolved issues so that factor replacement therapy can be optimized, based on evidence.

Keywords: haemophilia, clotting factor, dose, response.

The aim of treatment in haemophilia is to favourably alter the deranged haemostasis so that spontaneous bleeding is prevented and its resultant complications avoided (Mannucci, 2003). This has been achieved so far by replacement of the deficient factor. Ideally, one would use the least amount of factor concentrate required to achieve the desired end point of care in the common indications for replacement therapy: prevention and treatment of joint and soft tissue bleeding, surgery and induction of immune-tolerance. The management of haemophilia has improved greatly in the last three decades (Berntorp *et al*, 1995). This has been achieved by early recognition and diagnosis combined with replacement of high doses of factor concentrates to treat this condition effectively. In this process, however, haemophilia has become one of the most expensive diseases to manage today (Bohn *et al*, 1998; Harper *et al*, 2003). Both from a scientific and economic point of view (Schramm & Berger, 2003), it is important that factor replacement therapy, which accounts for more than 90% of the cost of care (Miners *et al*, 1998), be rationalized, based on evidence. This article will review the data available in the English literature on the correlation of outcome with different doses of factor replacement for management of musculoskeletal bleeding and surgery. As there are excellent recent reviews on the management of patients with inhibitors and immune-tolerance induction (DiMichele, 2003; Paisley *et al*, 2003), these topics will not be included in this review.

Treatment and prevention of bleeding into joints/soft tissue

Although the benefit of blood transfusion in haemophilia was established in the mid-19th century (Lane, 1840), it was not until a century later that the basis for this response was gradually understood (Brinkhous *et al*, 1954). This approach was limited by problems associated with availability, storage, accessibility and volume of infusion. The situation changed with the discovery of cryoprecipitate in 1964 (Pool *et al*, 1964). It was then possible to achieve higher plasma levels without volume overload (Hattersley, 1966; Bloom & Emmanuel, 1968; Dallman & Pool, 1968). Once plasma could be fractionated to produce lyophilized clotting factor concentrates (CFC), prophylactic replacement of clotting factors became possible. The concept was first initiated in 1958 in Malmo, Sweden (Nilsson *et al*, 1970). Two modes of replacement therapy thus evolved: one where CFC was administered as soon as bleeding occurred (on-demand) and the other where it was administered to prevent bleeding (prophylaxis). Over the last four decades, considerable clinical experience in many countries with intensified replacement therapy has shown that the natural history of severe haemophilia can be significantly altered by both of these approaches.

On-demand therapy

In the 1950s, factor replacement for bleeding was achieved by transfusing whole blood or plasma (Brinkhous, 1964; Biggs,

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1967). With the ability to assay clotting factor levels from the early 1950s (Langdell *et al*, 1953), it was possible to measure the effect of a particular dose of plasma. Brinkhous (1964) and colleagues in USA and Biggs (1967) in the UK made the first efforts towards establishing a dose–response relationship. Their observations suggested that levels as low as 5% were sufficient for clinical response in acute haemarthoses but levels above 25% were needed for control of surgical bleeding. It was also noted that even with levels of 12–20%, which could be achieved with plasma infusion, 96% of acute haemarthroses could be successfully treated (Roberts *et al*, 1964). When cryoprecipitate became available after 1964, higher doses (10–20 IU/kg) could be used and early treatment could be initiated, even at home, with better results (Britton *et al*, 1974; Ashenhurst *et al*, 1977; Biggs, 1977; Ingram *et al*, 1979). Based on clinical observation of responses to treatment, a dose of 20 IU/kg was recommended for the treatment of acute bleeding episodes (Honig *et al*, 1969). This was challenged by several groups showing that a lower dose appeared to be equally effective, based on responses obtained to factor replacement for acute joint bleeding at camps. Penner and Kelly (1977) evaluated three doses of 7–9, 11–13 and 15–17 IU/kg and reported success in 90%, 79% and 94% of episodes treated respectively. This was similar to that reported with >20 IU/kg. Successful treatment was defined as clinical resolution of that bleed with one dose of treatment. The high success was attributed to replacement being administered very soon after the bleed. This was corroborated by similar reports from Seeler *et al* (1975) and Ripa *et al* (1978) in patients with severe deficiency of both factor VIII (FVIII) and IX (FIX). Weiss (1977) compared two doses and reported successful control of bleeding in 89% of acute haemarthroses when doses aimed at achieving 15–25% levels were used while it was 94% when doses aimed to achieve 25–40% levels were used.

Allain (1979) attempted a systematic evaluation of the efficacy of replacement therapy in 70 children receiving FVIII as cryoprecipitate at doses varying between 10–31 IU/kg. He showed that FVIII levels of 28%, 35% and 53% resulted in successful treatment of 90%, 95% and 99% of bleeding episodes respectively. Aronstam *et al* (1980) reported two randomized double-blind studies conducted for evaluating response to different doses of CFC in acute joint bleeding. In the first study, they compared outcome of therapy with 7, 14, 28 IU/kg for knee, elbow and ankle bleeds. More than 90% of bleeds were treated within 2 h of onset. Their data showed that while the response to 14 IU/kg was superior to 7 IU/kg, the dose of 28 IU/kg was not obviously superior to the lower doses, in terms of time for resolution of bleeds in any of the three joints. In the second study, they compared the outcome in patients receiving replacement therapy, more than 3 h after bleeding, to achieve 20% or 40% factor level after joint bleeds resulting in >50% loss of baseline movement (Aronstam *et al*, 1983). All these patients had significant pre-existing arthropathy. No difference was found between the two groups in the number of infusions needed and time in hospital but functional restoration was better in those receiving the higher dose. These data suggest that if CFC replacement is done early, as should be possible with home therapy, doses <20 IU/kg could achieve responses similar to that with doses >20 IU/kg in most patients. This is likely to be even more so if treatment is given for joints that have no or minimal pre-existing damage. It will be important to evaluate long-term outcome with prophylactic replacement of CFC at these doses.

Table I shows a summary of studies on treatment of joint bleeding with lower doses of factor replacement reported between the late 1960s and early 1980s (Brown *et al*, 1967; Honig *et al*, 1969; Britton *et al*, 1974; Abildgaard, 1975; Ashenhurst *et al*, 1977; Penner & Kelly, 1977; Weiss, 1977; Ripa *et al*, 1978; Allain, 1979; Stirling & Prescott, 1979; Aronstam *et al*, 1980, 1981, 1982). Most investigators used dosage between 10–20 IU/kg and reported successful treatment in 75–100% of cases. Lower success rates, between 55% and 65%, have been reported with doses >20 IU/kg reflecting the difficulties in comparing bleeds and their assessment in haemophilia (Brown *et al*, 1967; Aronstam *et al*, 1980). It is notable that these response rates are similar to more recent studies with recombinant CFC using 25–40 IU/kg/bleed (Bray *et al*, 1994; Abshire *et al*, 2000; Courter & Bedrosian, 2001; Rothschild *et al*, 2002).

After the early 1980s, there was a remarkable lack of any significant effort at evaluating dose and response to factor replacement therapy in haemophilia. It is quite likely that the trauma caused by human immunodeficiency virus infection in this community completely shifted the focus of attention from dose and response to safety and supply of factor concentrates (Rickard, 1990). However, in an international landmark study soon after that period, Aledort *et al* (1994) correlated the effect of dose with long-term orthopaedic outcome in severe haemophilia. Patients received <12, 12–25, 25–40 or >40 IU/kg/bleed. Although detailed data on dosage was not reported, long-term outcome was shown to be best in the group receiving 25–40 IU/kg, in terms of change of radiological scores from baseline. Why those patients receiving >40 IU/kg/bleed did not fare equally well or better was not clear. The average age in this study was 13·5 ± 6·6 years with an average physical examination joint score of 6·05 ± 6·58 at entry. This shows that the study included relatively older children/young adults with significant pre-existing joint damage. Whether the results would be different if younger children with no or minimal joint changes were given lower doses soon after joint bleeding and followed up long-term is again not known. Based on their data, Aledort *et al* (1994) concluded that higher doses of factor concentrates by themselves do not necessarily produce better orthopaedic outcome.

Thus, it appears that when plasma was the mainstay of replacement therapy, doses of 10–20 IU/kg were considered sufficient and effective. With the availability of concentrates in

Table I. Summary of reports describing outcome of lower doses of factor replacement for acute haemarthroses.

Study	Types of bleed	Therapeutic material	Dose (IU/kg)	Success rate (%)
Brown *et al* (1967)	Haemarthroses	Cryoprecipitate	23	56–64
Honig *et al* (1969)	Haemarthroses	FVIII concentrate	20–30	92
Britton *et al* (1974)	Haemarthroses	FVIII concentrate	10	97
Abildgaard (1975)	Haemarthroses	FVIII concentrate	10	96
Ashenhurst *et al* (1977)	Haemarthroses	FVIII concentrate	8–12	100
	Other			
Penner and Kelly (1977)	Haemarthroses	FVIII concentrate	7–9	90
			11–13	79
			15–17	94
Weiss (1977)	Haemarthroses	FVIII concentrate	7·5–12·5	89
	Other		12·5–20	94
Ripa *et al* (1978)	Haemarthroses	FVIII/FIX concentrate	3–7	100
Allain (1979)	Haemarthroses	Cryoprecipitate	31	99
	Other			
Stirling and Prescott (1979)*	Haemarthroses	FVIII concentrate	5·7	85
			3·0	71
Aronstam *et al* (1980)*	Haemarthroses	FVIII concentrate	7	67
	(knee, severe)		14	95
			28	100
Aronstam *et al* (1981)	Haemarthroses	FVIII concentrate/others	11–16	78
Aronstam *et al* (1982)	Haemarthroses	FVIII concentrate	7	89
			14	77

*Randomized trials.

large quantities, there has been a more liberal approach to replacement therapy (25–40 IU/dose) aimed at achieving higher levels of 50–80% without adequate evidence to support such a practice.

Prophylactic factor replacement

The concept that the prevention of bleeds was possible and desirable evolved in the late 1950s in Sweden and was supported by the clinical observation that patients with moderate haemophilia, with factor levels of 1–5%, had only occasional spontaneous bleeding and therefore maintained good joint integrity (Nilsson *et al*, 1970). Their experience then encouraged others to initiate this practice (Bellingham *et al*, 1967; Biggs, 1967; Shanbrom & Thelin, 1969; Hirschman *et al*, 1970; Kasper *et al*, 1970; Nilsson *et al*, 1970; Van Creveld, 1971; Ramsay & Parker, 1973; Le Quesne *et al*, 1974; Morfini *et al*, 1976). These investigators showed that prophylactic factor replacement could markedly reduce the incidence of acute haemarthoses. However, widely varying doses were used during this time, ranging from 300 IU every 2–4 weeks to 70 IU (one unit of cryoprecipitate) given twice daily. Aronstam *et al* (1976) reported the only double-blind trial in the literature on prophylactic factor replacement in haemophilia. They compared the efficacy of factor replacement to achieve 25% levels once a week with a dose that would not raise it beyond 1%. This was evaluated in nine patients with severe haemophilia aged 14–18 years, all with significant pre-existing joint damage. In a cross-over design, each patient was randomly assigned to either of the two arms, at the beginning of the study. In those receiving the higher dose, bleeding frequency in the first 3 d after infusion was reduced by 66% but overall there was only 15% reduction in bleeding episodes. While the doses selected can now be questioned, the design of the study is remarkable. Similar studies comparing doses more likely to be successful in controlling acute joint bleeding are needed.

Two groups have reported long-term observational data on the efficacy of primary and secondary prophylactic replacement of CFC. The first of these reports was from Sweden and described the outcome of prophylactic treatment over 25 years (Nilsson *et al*, 1992). Three cohorts of patients, divided according to age at which prophylaxis was started (6·5, 2·5 and 1·2 years), were followed-up for up to three decades. The last group ($n = 21$) was most intensively treated, with 25–40 IU/kg doses three times a week for haemophilia A and twice a week for haemophilia B aimed at maintaining trough factor levels of >1% at all times. The best outcome was achieved with early initiation of high-dose prophylaxis. At the time of the first report, children in the last group, who had received mean annual doses varying between 4100 and 9600 IU/kg, had no joint damage detectable clinically or radiologically. In a follow-up to this report, Lofqvist *et al* (1997) reported that 79% of those initiated on

intensive prophylaxis between 1 and 4·5 years of age with the doses mentioned above had zero joint scores by 7–22 years of age ($n = 34$). These data are impressive evidence of the efficacy of high-dose prophylaxis. It is also obvious that even at these doses, there can be a twofold variation in the amount of CFC usage among patients in the same cohort to achieve similar end points. However, they do not show whether there was any significant difference in the functional ability or the health related quality of life (QOL) between this cohort and those having a clinical joint score of ≤2 and radiological score of ≤7. This is important because those with minimal changes used almost half the doses as those who had no radiological changes. Such high doses are associated with costs that are prohibitive even in many developed countries. Using lower doses, Petrini (2001) has reported that children who have <1% factor levels on prophylaxis do not necessarily bleed more frequently than those maintaining >1% at all times. Therefore increasing doses to achieve >1% trough levels at all times may not be necessary in many patients. Since the number of bleeds per year is one of the major determinants of long-term outcome and not the factor level itself, it is very likely that such an approach may not lead to an adverse outcome of musculoskeletal function while avoiding escalation of doses (Fischer *et al*, 2002). It would be very interesting to see whether bleed frequencies, joint scores, functional ability and QOL of comparable patients treated at these two centres in Sweden differ significantly.

Detailed data on long-term outcome of musculoskeletal function in haemophilia has also been reported from the Netherlands (van den Berg *et al*, 2001, 2002). This data is particularly useful as it provides information on the evolution of joint status at different replacement doses of CFC practiced from the 1970s to 1990s. Patients born in the late 1970s were treated with doses of 5–10 IU/kg two to three times a week for haemophilia A using cryoprecipitate and intermediate purity CFC. Those born in the early 1980s received doses of 10–20 IU/kg and those born in the late 1980s, 20– 40 IU/kg at the same frequency. The mean age of starting prophylaxis decreased from 4·6 to 3·9 years during this period. The total dose/year increased from about 1800 to 2900 IU/kg with weekly doses changing from 16 to 33 IU/kg. Evaluation of musculoskeletal function at 19·6, 14·7 and 7·9 years respectively, showed that the mean clinical joint scores were 2·0, 0·9 and 0·2 and the mean radiological joint scores were 6·1, 2·3 and 1·1 (Table II). Fischer *et al* (2001) reported similar data correlating the impact of intensification of treatment over the last three decades on the outcome of musculoskeletal function in the entire population of people with haemophilia treated at the van Creveldklienik, including those on on-demand therapy. The median annual dose for prophylaxis changed from 886 IU/kg in the 1970, to 1514 IU/kg in the 1980s and 1818 IU/kg in the 1990s (Table III). In these cohorts, the median number of joint bleeds/year was 7·7, 5·5 and 2·8, with the annual changes in Pettersson score being 1·0, 0·7 and 0·4 respectively. Although these joint scores appear different, they represent cohorts at different ages. What the scores will be in the youngest cohort when they reach the age of the older cohorts remains to be seen. It will be good if these investigators analyse and report this at a later date.

Table II. Characteristics of the patients on prophylaxis.

	Group 1	Group 2	Group 3
Year of birth	1974–79	1980–85	1986–90
Number	21	22	27
Age (years) at last visit*	21 (0·4)	15·5 (0·4)	10·1 (0·3)
Age (years) at start of prophylaxis*	4·6 (0·7)	4·0 (0·5)	3·9 (0·3)
Age (years) at first joint bleed*	2·1 (0·2)	2·9 (0·4)	2·3 (0·3)
Annual number of joint bleeds*	5·3 (1·4)	3·2 (0·9)	2·6 (0·6)
Time between first joint bleed and start of prophylaxis (years)*	3·0 (0·5)	2·3 (0·4)	1·9 (0·3)
Pettersson score*	6·1 (1·9)	2·3 (0·6)	1·1 (0·4)
Age (years) at time of Pettersson score*	19·6 (0·6)	14·7 (0·4)	7·9 (0·4)
Orthopaedic joint score*	2·0 (0·6)	0·9 (0·4)	0·2 (0·2)
FVIII consumption (IU/kg/year)	1828	2145	2900

*Data are shown as mean (SE).
From van den Berg *et al* (2001), reproduced with permission of Blackwell Publishing.

In a comparison of outcome at different doses van den Berg *et al* (2003), compared the outcome of treatment at intermediate doses of prophylaxis (1828 IU/kg/year) in the Netherlands with higher doses (3713 IU/kg/year) used in Sweden in age-matched patients. The mean radiological scores were 2·0 and 2·4 in these two cohorts evaluated at about 20 years of age in spite of the Swedish cohort receiving double the quantity of CFC. It may be reasonable to conclude that increasing the CFC dose beyond a certain level does not necessarily translate to better joint scores. Another extremely relevant issue is the actual impact, if any, of these slightly different scores on the functional ability and QOL of these individuals. At low scores of ≤2, it would be important to know if there was any significant difference in these parameters to justify the approximately 1000 IU/kg difference in annual CFC usage.

Current studies

Three groups are currently evaluating different aspects of prophylactic replacement of CFC in prospective trials. The Italian study (ESPRIT) is aimed at a randomized comparison of prophylaxis *versus* intensive on-demand therapy (Gringeri, 2003). Patients in the on-demand arm will receive doses of 25 IU/kg or more for each bleed while those on prophylaxis will receive 25 IU/kg three times a week. This is the first such randomized comparison after Aronstam *et al* (1976) and is therefore a critical study but only 45 patients have been enrolled for randomization. After excluding drop-outs,

Table III. Treatment characteristics of all patients with severe haemophilia born 1944–94, treated at the Van Creveldkliniek over the last three decades.

	1970s	1980s	1990s
Number of patients	112	181	211
Total number of patient years	539	1356	1672
Age (years)	15·9 (10·1–20·1)	20·5 (11·9–27·8)	24·9 (14·0–35·0)
Age at first treatment (years)	1·4 (1·0–2·2)	1·0 (0·7–1·2)	1·1 (0·8–1·6)
Age at start of home-treatment (years)	17·3 (14·0–23·0)	12·2 (6·5–21·1)	6·7 (4·0–11·8)
Age start of prophylaxis (years)	13·3 (8·0–17·8)	6·4 (4·0–13·7)	4·7 (3·1–8·4)
Percentage on home treatment (%)	21	67	90
Full prophylaxis (%)/on demand (%)	35/55	57/31	63/28
Weekly prophylatic dose (IU/kg)*	16 (11–22)	26 (20–35)	33 (24–45)
Clotting factor consumption			
Annual use prophylaxis (IU/kg)	886 (632–1259)	1514 (1160–2031)	1880 (1402–2538)
Annual use on demand (IU/kg)	207 (67–444)	238 (88–532)	359 (146–772)
Outcome			
Joint bleeds/year on prophylaxis	7·7 (4·0–16·4)	5·5 (3·4–13·1)	2·8 (2·0–10·1)
Joint bleeds/year on on-demand	7·5 (2·3–15·0)	6·5 (2·0–13·3)	5·1 (1·3–11·0)
Change in Pettersson score (patients/year)	1·0 (0·6–1·4)	0·7 (0·2–1·6)	0·4 (0·1)

Values are given as numbers, percentages or medians (interquartile ranges).
Adapted from Fischer *et al* (2001) with permission of Blackwell Publishing.
*Data for patients with haemophilia A.

36 patients can be analysed for long-term outcome, with 33 of them being on the original study protocol. The final analysis is awaited.

The second study is also a randomized clinical trial being conducted in the USA to compare aggressive 'on-demand' factor replacement (doses of 40 IU/kg at onset of haemorrhage followed by 20 IU/kg at 24 and 72 h and 20 IU/kg every 48 h for up to 4 weeks until joint function is completely restored) with alternate day prophylaxis (25 IU/kg/dose) (Manco-Johnson & Blanchette, 2003). The aim is to determine whether prevention of chronic joint damage requires prevention of bleeding events or can be achieved by promoting complete resolution of each joint bleed. Sixty-five children with severe haemophilia have been enrolled into this study that has an excellent compliance of 98%. Follow-up will be completed in September 2005 in this important study.

The third is a Canadian study which is a single-arm open label trial of escalating dose prophylaxis (Manco-Johnson & Blanchette, 2003). Beginning with 50 IU/kg once a week, doses can be escalated to 30 IU/kg twice a week or 25 IU/kg three times a week, if there are three or more haemorrhages into a single joint or four clinically-determined significant soft tissue or joint haemorrhages affecting any site in a 3 month period. Twenty-five children have been recruited and followed up for 5 years. Outcome analysis is awaited but the small number of patients in each arm is likely to be a significant limitation of the data.

While these studies have all addressed crucial problems, their greatest limitation is the small number of patients recruited. Multicentre studies capable of recruiting large numbers of patients and designed to provide the answers to many unresolved questions are essential (Berntorp *et al*, 2003). The major issue with regard to prophylaxis therefore is whether similar efficacy can be achieved at lower doses with a better cost-benefit ratio (Ljung, 1998). It is clear that outcome certainly improves with higher levels of factor replacement and that early prophylactic administration of CFC is superior to on-demand treatment. However, most of these reports are based on observational data where dosage depended on the practice of the era rather than comparison of doses. Doses of CFC that are currently used have never been evaluated in randomized trials. Based on many of the early studies, there seems to be reasonable evidence in the literature that doses of 10–25 IU/kg/dose give excellent responses in acute joint bleeding even with pre-existing arthropathy. This could be even better in joints without such damage. This is the dose that is worth evaluating in long-term prospective trials on prophylaxis. There is little evidence for the 25–40 IU/kg/dose being commonly used at present.

Surgery in haemophilia – optimal dose for haemostasis

Successful haemostasis for surgery in people with haemophilia was reported from different parts of the world in the late 1960s (Fessey & Meynell, 1967; Wilson & Staveley, 1967; Bloom *et al*, 1968; Kemp & Matthews, 1968; Kwa, 1968; Gaum, 1969). At that time, it was a significant step forward from a situation where minor injuries could lead to life threatening complications to a position where major elective surgery could be performed with adequate haemostasis. Over the next 30–40 years, the situation has improved to the extent that any surgical procedure can now be performed in patients with haemophilia. No attempt has, however, been made to evaluate the optimal dose needed to achieve postoperative haemostasis. The result is a complete lack of uniformity in practice in this field, with almost as many protocols for factor replacement as

there are centres performing surgical procedures. There are also differences in the mode of factor replacement for postoperative haemostasis: intermittent bolus infusions (BI) or continuous infusion (CI). CFC has traditionally been administered by BI of the dose calculated to achieve the desired levels and timed according to the expected half-life of the product. While this is easier to do, it leads to high peak and low trough levels. This is a disadvantage, particularly in the postoperative situation, where inordinately low levels could result in bleeding, particularly if doses are missed. To avoid such troughs, much higher than required peaks are aimed for, resulting in wastage of CFC. These problems can be avoided using CI of CFC to maintain steady state plasma levels (Schulman, 2003). Both these methods of administering CFC continue to be widely used. However, most CFCs do not have regulatory approval for use by CI. This could be a reason why this modality of administration is not used as often as it could be, apart from the need for infusion devices for setting it up.

Table IV. Protocols for factor replacement for orthopaedic surgery in haemophilic patients.

	FVIII%	FIX%
(a) At Malmo, Sweden (data from Lofqvist *et al*, 1996)		
Preoperative	100–140	60–70
Days 2–7	30–40*	30–40‡
Days 7+	10–20†	10–20§
(b) At Vellore, India (Srivastava *et al*, 1998¶)		
Preoperative	80–100	60–80
Days 2–4	20–40	15–30
Days 5+	15–30	10–20

Levels refer to peak and trough. FVIII administered q12 H and FIX q24 H.

FVIII: 50–70 IU/kg preoperative; *20–40 IU/kg q4–8h; †10–15 IU/kg q12h.

FIX: 60–70 IU/kg preoperative; ‡40–60 IU/kg q12–24H; §10–20 IU/kg q24–48h.

¶From Srivastava *et al* (1998), reproduced with permission of Blackwell Publishing.

Factor replacement by intermittent bolus infusion

The first reports of surgical procedures performed in haemophilia patients were published in the 1970s (Adeloye & Oluwasanmi, 1972; Rudowski & Ziemski, 1972; Krieger *et al*, 1977; Nilsson *et al*, 1977; Houghton & Dickson, 1978). Protocols for factor replacement were described in detail in some of these publications. Krieger *et al* (1977) aimed at achieving 100% levels for surgery followed by levels >60% during the first 4 d and then >40% until suture removal. With this approach bleeding was noticed in 5–10% of cases and mortality was <1% in most series. Rudowski (1981) described surgery performed on 110 patients between 1961 and 1980. Among them, 11% of them had haemorrhagic complications and 4·5%, suffered haemorrhage-related mortality. The actual level achieved for surgery seemed to vary but averaged about 60%, followed by >30% level being maintained postoperatively until the wound had healed.

In the largest series of surgical procedures in haemophilia, Kasper *et al* (1985) described the first attempt at correlating postoperative bleeding with factor levels. Among 163 patients who underwent 350 surgical procedures between 1967 and 1983, 23% had haemorrhagic complications, 72% of which were with factor levels >40% and only 15% with factor levels under 30%. The mortality was 0·6%. Preoperative factor levels were raised to 80–120% and levels >30% were maintained postoperatively for 10 d or until the wound had healed. A comparison of factor usage and mean trough levels during the first postoperative week was done for different time periods. During 1967–72, the mean total dose used per procedure was 600 IU/kg. This increased to 1300 IU/kg during 1975–79, followed by 2000 IU/kg during 1980–83. The mean trough level also increased from 39% to 73% during this period but there was no change in the rate of bleeding complications. It was concluded that factor levels were not the sole determinants of postoperative bleeding in haemophilia. In another large series, Kitchens (1986) described a series of 65 patients who underwent 100 procedures between 1977 and 1984, with 6% haemorrhagic complications but no haemorrhage-related mortality. This group also aimed for 80–100% levels for surgery and >30% level during the postoperative period for 14 d. The most recently published large series of surgery in haemophilia is from Sweden. Lofqvist *et al* (1996) reported their experience with orthopaedic surgery in haemophilia over 20 years – a total of 98 procedures on 66 patients. The target factor levels mentioned in this report are among the lowest described in the literature (Table IVa). However, the actual range of dosage of CFC used (400–2300 IU/kg) suggests that higher levels were maintained in some cases. Since the details of use of CFC in individual patients were not described, this is difficult to confirm. That postoperative haemostasis is possible with such doses is supported by data from India. Based on their early experience over 10 years between 1984 and 1993 Bhushan *et al* (1994) and Srivastava *et al* (1998) have shown in a series of 18 patients undergoing 22 surgical procedures, with some patients having simultaneous multiple procedures, that levels even lower than those suggested by the Malmo group (Table IVb) can be practiced without increasing the risk of complications significantly. Haemostasis was maintained in these patients with about 300 IU/kg of CFC. There was a 5% incidence of postoperative haemorrhage but no haemorrhage-related mortality. This has been confirmed in other reports as well (Ghosh *et al*, 1998; Srivastava *et al*, 1999). It should be noted, although, that these series did not include patients requiring joint replacement surgery.

Table V lists the major reports describing factor replacement by BI for surgery in haemophilia (Krieger *et al*, 1977; Rudowski, 1981; Kasper *et al*, 1985; Brown *et al*, 1986; Kitchens, 1986; Yue & Mann, 1986; Bhushan *et al*, 1994; Lofqvist *et al*, 1996; Ghosh *et al*, 1998; Srivastava *et al*, 1998,

Table V. Summary of reports of surgery in haemophilia using bolus infusion of clotting factor concentrates.

Report	Type of disorder/ number of patients	Number and types of surgery	Preoperative factor level (%)		Factor level (%) postoperative		Total FVIII/ procedure (IU/kg)†	Total FIX/ procedure (IU/kg)†	Postoperative bleeding (%)
			FVIII	FIX	FVIII	FIX			
Krieger *et al* (1977)	HA/28 HB/6 others/8	94; Orthopaedic, gastrointestinal, general surgical, others	100	100	60 (day 1–4)* 40 (day 5 onwards)	60 (day 1–4)* 40 (day 5 onwards)	NR	NR	6
Rudowski (1981)	HA/85 HB/16 Others/9	131; Orthopaedic, general surgical, others	NR	NR	NR	NR	661*	802	11‡
Brown *et al* (1986)	HA/18 HB/4	23; Abdominal, general surgical	100	100	50 (day 1–7) 20–25 (day 7–10)	35	NR	NR	18
Kasper *et al* (1985)	HA/163	350; Orthopaedic, gastrointestinal, general surgical	84 (1967–1972) 122 (1973–1974)	NA	39 (1967–1972) (day 1–14) 73 (1980–1983) (day 1–14)	NA	600 (1967–1972) 1000 (1973–1974) 1300 (1975–1979) 2000 (1980–1983)	NA	23
Yue and Mann (1986)	HA/9	10; Neurological	100	NA	100 (day 1–3) 50 (day 4–10)	NA	NR	NA	NIL
Kitchens (1986)	HA/51 HB/10	100; Orthopaedic, gastointestinal, general surgical, others	78	55	NR	NR	NR	NR	6
Bhushan *et al* (1994)	HA/32 HB/5 Others/15	59; Orthopaedic, general surgical, others	80	50–80	20–40 (upto 10 d)	15–30 (upto 10 d)	NR	NR	24
Lofqvist *et al* (1996)	HA/53 HB/13	98; Orthopaedic	50–150	50–150	30–40 (day 1–7) 20–30 (day 8–24)	30–40 (day 1–7) 20–30 (day 8–24)	1596	–	NR
Shapiro *et al* (1997)	HB/74	81; Orthopaedic, gastointestinal, general surgical, others	NA	60–100	NA	>30 (day 1–10)	NA	703	NIL
Srivastava *et al* (1998)	HA/11 HB/7	20; Orthopaedic, gastrointestinal, general surgical, others	80–100	60–80	20–40 (day 1–3) 15–30 (day 4+)	15–30 (day 1–3) 10–20 (day 4+)	260	300	5
Ghosh *et al* (1998)	HA/12 HB/4	16; Orthopaedic, general surgical, others	60–100	60–100	30–80	30–80	587	453	12·5
Srivastava *et al* (1999)	HA/22 HB/7	31; Orthopaedic, gastrointestinal, general, others	85	90	37 (day 2–3) 23 (day 6–7)	27 (day 2–3) 13 (day 6–7)	268	299	9
Scharrer *et al* (2000)	HA/15	22; Orthopaedic, general surgical, others	NR	NA	NR	NA	984	NA	NR

HA, haemophilia A; HB, haemophilia B; BI, bolus infusion; FVIII C, FVIII coagulant activity; FIX: C, FIX coagulant activity; NR, not reported; NA, not applicable.
*Factor replacement using fresh frozen plasma (FFP) and cryoprecipitate (CP).
†Mean dosage.
‡4·5% mortality related to haemorrhage.

1999; Scharrer *et al*, 2000). It can be concluded that the overall data in the literature suggests that with BI, adequate surgical haemostasis can be achieved by 80–100% levels during surgery, and >30% levels in the postoperative period until wound healing, with perhaps slightly higher levels of 40–50% in the first 3–5 d. In the meantime, current consensus recommendations continue to advocate much higher levels (Berntorp *et al*, 1995). It is also the practice in many centres around the world, as has been reported in an on-going survey of factor replacement protocols for surgery in haemophilia on behalf of the International Society on Thrombosis and Haemostasis (Srivastava, 2003a).

Factor replacement by continuous infusion

Although CI of factor concentrates was described as early as 1970 (Mcmillan *et al*, 1970), its wide application for factor replacement by CFC in the postoperative period has mainly occurred over the last decade. Martinowitz *et al* (1992) showed that a significant reduction in the total quantity of CFC used for major surgery could be achieved by administering CFC as adjusted-dose CI. In this method, target levels are achieved by adjusting the dose of infusion of CFC every day, taking into account the clearance of FVIII on that day and not following a fixed dose of infusion. Among eight patients undergoing major elective surgery in this report, the total dose of CFC was about 450 IU/kg, about half the amount that would be used with standard doses of BI. Target factor levels were 50% during the first week and 30% during the second week. No patient had any bleeding complication. In a comparison of CI with BI, Batorova and Martinowitz (2000) targeted 50% level on postoperative days 1–4, 40% on days 5–7 and 30% thereafter. The mean total dose used was 467 IU/kg in the CI group and 733 IU/kg in the BI group. While no unexpected bleeding occurred among those receiving CI, 17% of those receiving BI had complications related to bleeding. Tagariello *et al* (1999) reported a similar experience using fixed doses for CI, 3 IU/kg/h for 10 d followed by 1·5 IU/kg on subsequent days. No bleeding complications were noted among 15 patients. In comparison, among historical controls receiving BI, 31% required additional treatment for bleeding complications. These are unusually high figures for postoperative bleeding, even with BI, and are difficult to explain. More recently, Dingli *et al* (2002) reported the outcome of surgery in 28 patients with haemophilia who underwent 45 procedures. This group aimed at much higher factor levels, maintaining 100% for 2–5 d followed by 50% thereafter for 5–14 d by CI. In spite of factor levels ranging between 46% and 191% among these patients, 11% had bleeding complications. All of these occurred with factor levels of 55–161% during those episodes.

Table VI lists the major reports that described factor replacement with CI for surgery in haemophilia (Martinowitz *et al*, 1992; Hay *et al*, 1996; Campbell & Rickard, 1998; Rochat *et al*, 1999; Schulman *et al*, 1999; Tagariello *et al*, 1999; Batorova & Martinowitz, 2000; Mackinlay *et al*, 2000; Dingli *et al*, 2002; Ragni *et al*, 2002; Hoots *et al*, 2003). The details are inadequate in many of the reports but confirm that there is little consensus on the dosage of CFC to be used for surgery in haemophilia. With variable doses and total factor consumption in the range of 800–1500 IU/kg per procedure, haemorrhagic complications still occur in about 5–10% of cases.

It is again obvious that prospective studies are needed to evaluate different dosing regimens in different types of surgical procedures. However, apart from the dose and mode of administration of CFC for surgery, many other issues remain unresolved. These include the interval between doses for BI, the number of days of replacement therapy necessary for different types of surgery, frequency of monitoring factor levels after surgery, use of adjuvants, such as antifibrinolytic drugs and fibrin sealant, and their correlation with the incidence of complications – haemorrhage, thrombosis, infections and inhibitor formation. To address these issues, an international survey of practices and outcome is currently being conducted (Srivastava, 2003a) to collect as much information as possible and formulate a consensus protocol that could then be prospectively evaluated. The ultimate goal should be to identify levels that are safe and not unduly high.

Dose and response – difficulties in haemophilia

It is standard therapeutic practice to assess the response to different dosages of any drug to determine an optimal dose and establish a therapeutic window that provides maximum efficacy with minimum toxicity. In addition, particularly for expensive therapy, this effort is also directed at achieving the highest cost-benefit ratio. These aims are easier to achieve for a drug that has a predictable composition, whose levels can be accurately assayed and the response to which can be quantified through an easily measurable parameter. The therapeutic efficacy is also better assessed if the end-points of treatment are well defined and can be reproducibly measured.

In haemophilia difficulties exist in all these aspects. First there was lack of suitable CFC in sufficient quantities for dose comparisons. Now that has been resolved but there are problems with significant variations in specifications and recoveries between products, both plasma-derived and recombinant CFC (DiMichele *et al*, 1996; Ewenstein *et al*, 2002). The difficulty is further compounded by the fact that there is considerable inter-laboratory variability in plasma activity assays (Preston *et al*, 2004). There are also difficulties in assessing and correlating clinical outcome with factor dosage and levels (Merchan, 2003). In acute joint bleeding, the quantum and severity is often difficult to quantify and measure reproducibly. The response to treatment is also most often measured by subjective parameters, such as relief of pain, swelling and tenderness, which are not easily quantifiable. The differences in responses reported by different investigators using similar doses of CFC perhaps bears testimony to this fact.

For the assessment of long-term outcome, clinical and radiological scores were developed (Pettersson *et al*, 1980;

Table VI. Summary of reports of surgery in patients with haemophilia using continuous infusion of clotting factor concentrates.

Report	Type of disorder/ number of patients	Number and types of surgery	Preoperative factor level (%)¶		Factor level (%) postoperative		Total factor VIII dose		Total FIX dose (IU/kg)	Postoperative bleeding (%)
			FVIII	FIX	FVIII	FIX	BI (IU/kg)	CI (IU/kg)		
Martinowitz *et al* (1992)	HA/18	18; Orthopaedic, abdominal, cardiac	80 (Major) 50 (Minor)	NA	50 (day 1–7) 30 (day 8–14)	NA	NA	447†	NA	NIL§
Campbell and Rickard (1998)	HA/18	18; (BI-8; CI-10); Orthopaedic	80–100‡	80–100‡	80–100 (day 1–3)*	50–80 (day 1–3)*	99 338 IU/patient	53 545 IU/patient	NA	20 (CI group) 88 (BI group)
Tagariello *et al* (1999)	HA/14 HB/1	15; Orthopaedic, gastrointestinal, others	100	100	29–121	25–50	NA	NR	NR	NIL
Schulman *et al* (1999)	HB/10	13; Orthopaedic	NA	50–100	NA	89 (day1) 80 (day2) 73 (day3)	NA	NA	663	NIL
Mackinlay *et al* (2000)	HA/6 HB/1	12; Cardiacsurgery, catheterization	100‡	100	80–100 (day 1–3) 30–60 (day 7–10) 20–40 (day 10–12)	50–80 (day 1–3) 30–40 (day 7–10) 20–30 (day 10–12)	93 000 IU/ patient	42 750 IU/ patient	99 000 IU/ patient	NIL
Batorova and Martinowitz (2000)	HA/40	43; (BI-18; CI-25); Orthopaedic, abdominal, others	50‡	NA	50 (day 1–4) 40 (day 5–7) 30 (day 8–12)	NA	733	467	NA	NIL (CI group) 17 (BI group)
Dingli *et al* (2002)	HA/28	45; Orthopaedic, cardiac, gastrointestinal	59–170	NA	100 (day 2–5) 50 (day 5–14)	NA	NA	NR	NA	11
Ragni *et al* (2002)	HB/28	36; (BI-27; CI-9); Orthopaedic, general, others	NA	63 (BI)‡ 106 (CI)	NA	80–100	NA	NA	385 800 IU/ patient	8·5
Hoots *et al* (2003)	HB/25	25; Orthopaedic, gastrointestinal, others	NA	90	NA	72–86	NA	NA	396	28

HA, haemophilia A; HB, haemophilia B; BI, bolusinfusion; CI, continuous infusion; NR, notreported; NA, notapplicable.

*Subsequent replacement as per Martinowitz *et al* (1992).

†Elective cases only.

‡Replacement by both bolus and continuous infusion.

§Tranexamic acid/fibrin glue used in all patients.

¶Aimed or achieved.

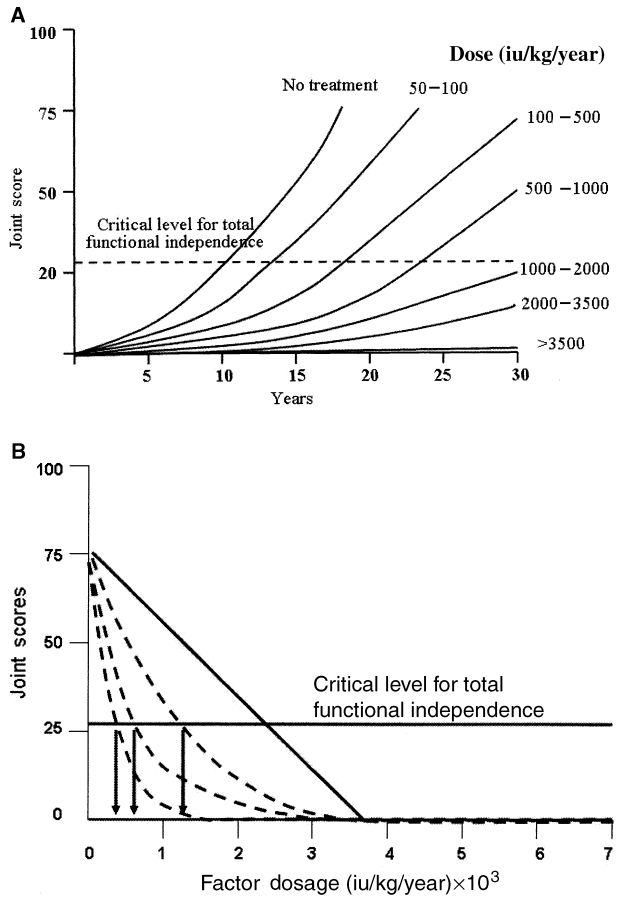

Fig 1. (A) Hypothetical correlation between age and joint score at different CFC replacement doses. (B) Hypothetical correlation between joint score and dose of CFC used.

Gilbert, 1993). These have been widely used in practice and in clinical studies. However, the clinical score has never been validated and the radiological score, although validated, lacks sensitivity and clinical correlation (Erlemann *et al*, 1987). Limitations with regard to inter-observer variability, ambiguity in definition and lack of clinical significance of certain parameters included in the scores have been noted (Hamel *et al*, 1988). Apart from these problems, there is also lack of data regarding their correlation with different dosages of CFC replacement (Srivastava, 2003b). Modifications of these scores have been suggested but have not been widely evaluated (Manco-Johnson *et al*, 2000). The International Prophylaxis Study Group is currently involved in developing validated scores for both clinical and radiological scoring (V. Blanchette, personal communication). Their clinical usefulness and wider acceptability remain to be seen. Long-term data is needed to correlate the outcome of musculoskeletal function with different dosages of CFC at different ages (Fig 1A) and determine whether this correlation is linear or parabolic (Fig 1B). This will be useful in establishing cost-effective models for factor replacement with CFC.

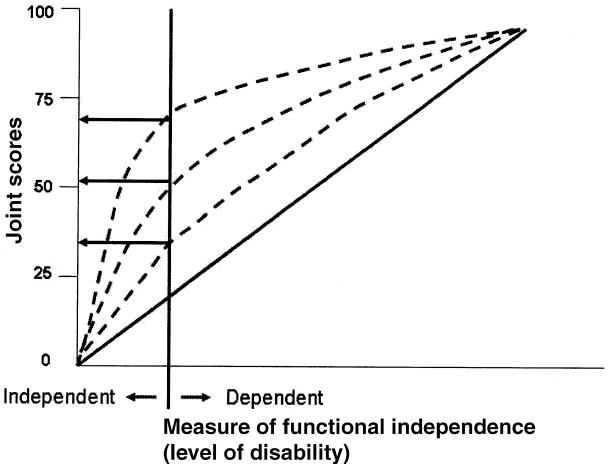

Fig 2. Hypothetical correlation between joint score and level of disability.

Another limitation of these scores is that they attempt to quantify changes in the joints alone, completely ignoring their correlation with function and overall disability, if any, in the individual. Outcome data in different studies is often compared with regard to minor changes in these scores. However, it is unclear what degree of change in these scores should be considered significant. Haemophilia-specific instruments for measuring scores of functional ability of individuals and their impact on health-related QOL are needed (Szende *et al*, 2003). These can then be used to define the level of change in the clinical and radiological scores that significantly impact these parameters (Fig 2). Finally, it will be important to decide whether the aim of CFC replacement therapy in haemophilia is to maintain normal (zero) clinical and radiological joint scores or good joint function, albeit with minimal joint scores. The difference in the cost of CFC used for these two approaches is likely to be very different, as is the cost-benefit ratio. This is obvious from data from Sweden and Netherlands (Lofqvist *et al*, 1997; van den Berg *et al*, 2003). The important message is that joint scores alone do not tell us enough about its impact on the life of the individual, particularly at very low scores. Therefore, the practical significance of minor differences in these scores is unclear and major therapeutic choices should not be based on these scores alone. The ultimate choice will depend on scientific evidence and socio-economic factors (Srivastava, 1999). While countries with less resource constraints may choose doses with highest response rates and lay less emphasis on cost-effectiveness, those with greater resource constraints may choose relatively lower doses. Having the appropriate data is important for both situations.

Conclusions

The data reviewed shows that current practices in haemophilia with regard to factor replacement therapy are clearly not

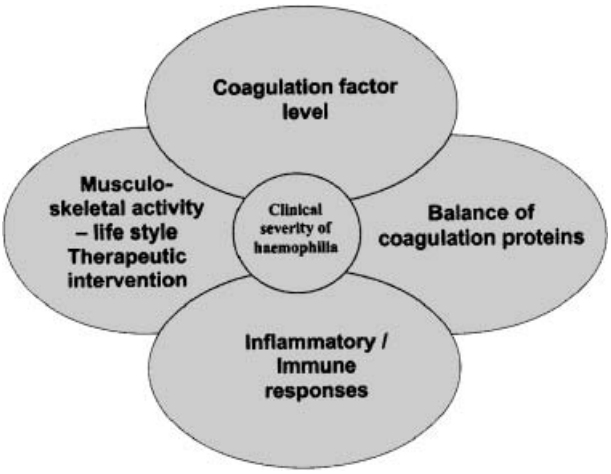

Fig 3. Factors contributing to the clinical severity of haemophilia.

evidence-based. Many factors have contributed to this situation. These include the small numbers of patients being seen in individual centres and lack of multi-centre studies; difficulties associated with the definition of the condition and allocation of severity based on factor assays, which themselves have intrinsic inconsistencies, particularly at the lowest levels (<1%); variability in the products used for treatment in terms of their recovery patterns and postinfusional assays; problems in comparison between patients because instruments used to measure outcome are imprecise and insensitive both with regard to clinical and radiological joint scores, and lack of disease specific instruments to measure outcome of musculo-skeletal function and health-related QOL.

It is also increasingly becoming clear that the phenotype of a disease is not determined by an abnormality of a single parameter (Beutler, 2001). In haemophilia too, it appears that the pattern of bleeding and musculoskeletal dysfunction is not determined by the level of the deficient factor alone but by a host of other determinants. These may include levels of other coagulation factors, prothombotic markers, and possibly polymorphisms of cytokines involved in the inflammatory response, apart from life-style and therapeutic interventions. The ultimate clinical phenotype is likely to be the result of all these interactions (Fig 3). Various studies are under way that will help unravel the role played by these factors in determining the result of therapeutic intervention. These will add new dimensions to the interpretation of data on the outcome of care in haemophilia.

In conclusion, there is inadequate data to produce evidence-based factor replacement protocols for haemophilia at this time. Large, multi-centre prospective studies need to be conducted so that enough patients can be recruited to answer the unresolved questions. This is no easy task and requires the determination of physicians and patients together to seek evidence for optimization of doses of CFC in the management of this condition.

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