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Aspects of haemophilia prophylaxis in Sweden

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Summary. Prophylactic treatment of haemophilia has been gaining acceptance as the optimal therapeutic option in an increasing number of haemophilia centres in the developed world in recent years. This paper focus on three aspects of prophylactic therapy: when to start treatment, venous access and the dose/dose interval. Evidence is in favour of prophylactic treatment to be started at an early age using either a peripheral vein

with 1–2 injections per week and a successive increase in the frequency depending on the child and the veins, or, using a Port-A-Cath which allows a better prophylactic coverage by infusions preferably every second day in haemophilia A and every third day in haemophilia B.

Keywords: haemophilia A, haemophilia B, factor VIII, factor IX

Introduction

There is no universal agreement on the definition of prophylactic therapy and on-demand therapy for haemophilia. The European Paediatric Network for Haemophilia Management, an informal group of 20 paediatricians from 16 western European countries, has suggested definitions on prophylactic treatment [1]. *Primary prophylaxis* is the regular, continuous treatment started before the age of 2 years or after the first joint bleed. *Secondary prophylaxis* is either a regular, continuous (long-term) treatment started at the age of >2 years or after two or more joint bleeds or a periodic (short-term) treatment due to frequent bleeds [2]. In a recent survey, this definition was used to assess the current therapeutic regimens for boys with severe haemophilia in the centres belonging to the Paediatric Network ($n = 18$ centres; $n = 1583$ patients) [2]. Seventy per cent of the boys at the centres were treated with continuous prophylaxis, either primary (39%) or secondary (31%), 9% were on periodic secondary prophylaxis and 19% on demand therapy (2% yet untreated). The differences between centres were pronounced when looking at the total population but with a trend towards prophylaxis since 16/18 centres would choose either primary or continuous secondary prophylaxis for a boy with newly diagnosed severe haemophilia.

This presentation will focus on three aspects of prophylactic therapy: when to start treatment, the dose/dose interval and venous access.

The Malmö model

In Sweden we have a long tradition of prophylactic treatment of haemophilia A and B [3,4]. The goal of the treatment is that the child should be able to live as normal life as possible. Prophylactic treatment is begun at 1–1½ years of age before the onset of joint bleeds, i.e. primary prophylaxis. Factor VIII (FVIII), 20–40 IU kg⁻¹ day⁻¹, is administered every second day or three times weekly in haemophilia A and Factor IX (FIX), 20–40 IU kg⁻¹ day⁻¹, every third day or twice weekly in haemophilia B. Almost all patients are on home treatment using a peripheral vein or a central venous line (Port-A-Cath, Pharmacia, Sweden). The dose and dose interval are optimized by means of pharmacokinetic studies. The same regimen is used for boys with moderate haemophilia with a clinically severe phenotype.

When should prophylactic treatment be started?

There are several studies on record concluding that prophylactic treatment is preferable to on-demand treatment [4–8] but even among adherents of primary prophylaxis, there are diverging views regarding the optimal regimen. Published reports by proponents of prophylaxis are characterized by the diversity of opinion as to when such treatment should be started. Some consider the ideal time to start treatment to be before

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Table 1. Three groups of boys studied during a 5-year interim at the Malmö centre [9]

	Group I: 16–22 years (<i>n</i> = 19)	Group II: 11–15 years (<i>n</i> = 9)	Group III: 7–10 years (<i>n</i> = 6)
Age at start of prophylaxis	2.6 (1.5–4.5)	1.3 (1–2)	1.2 (1–1.5)
Joint bleeds/year	2.2 (0–19.8)	0.1 (0–0.4)	0.4 (0–0.8)
Total annual dose IU/kg	3713 (2848–4619)	5741 (4730–7817)	6354 (5305–8915)
Radiologic score			
1990	4.8 (0–22)	0/0	0/0
1995	6.5 (0–31)	0/0	0/0
Orthopaedic score			
1990	1.2 (0–7)	0/0	0/0
1995	2.4 (0–18)	0/0	0/0

occurrence of the first joint bleed, which in practice means around the age of 1 year, when the child begins to walk [9,10]. The rationale for this view is twofold: to avoid the risk of a target joint developing, and to prevent other serious bleeds. At other centres, the occurrence of isolated joint bleeds before the start of prophylaxis is considered acceptable [4]. Evidence in support of an early start to treatment, at 1–2 years of age, derives from a recent study by Löfqvist and colleagues [9] who, in 1990 and again in 1995, investigated joint status in the 34 youngest children on prophylaxis at the Malmö centre (Table 1). Children who had developed target joints generally required higher dosages of factor concentrate in order to remain free from bleeding episodes, and were nonetheless at risk of joint deterioration, despite adequate prophylactic treatment. According to Kreuz and coworkers [10], even a small number of joint bleeds seemed to cause irreversible haemophilic arthropathy. Once apparent, further progression of joint damage could not be arrested even with prophylactic treatment. Table 2 summarizes their findings. The three groups in this study started prophylactic therapy at different ages but during the study period they received the same dosages. Despite this fact, joints already affected deteriorated during the study period.

One argument for accepting a few joint bleeds before starting prophylaxis is that it enables the child's proneness to bleeding episodes to be assessed and treatment to be adjusted accordingly. From earlier studies and clinical experience we know that approximately 10% of the severe haemophilia patients have infrequent bleeds. At some centres this may mean that on-demand treatment is given instead of prophylaxis. A further argument is that the later the start of regular injections, the better the chance of avoiding the need for a central venous catheter. However, in the series studied by Petterson

and coworkers [11], some patients already manifested joint changes at the start of prophylaxis, though they had had no clinically recognized joint bleeds. This suggests that subclinical bleeds may trigger the development of arthropathy in children with only isolated clinical bleeds, if the start of regular prophylactic therapy is delayed too long.

Astermark and coworkers [12] critically evaluated the Swedish series, 121 patients with severe haemophilia starting prophylactic therapy before the age of 10 years, and found that age at start of prophylaxis was an independent predictor for the development of arthropathy ($P = 0.0002$). It was found that those starting prophylaxis before the age of 3 years had a better clinical outcome in terms of arthropathy, i.e. there were significantly more boys with an orthopaedic score of zero, than those starting prophylaxis at the age of 3–5 or 6–9 years ($P = 0.001$). However, no significant difference was found between the latter two groups ($P = 0.275$). The dose and infusion interval at start and before the age of three were not an independent predictor for development of arthropathy in this study. Table 3 shows the effect of the dose interval when starting prophylaxis at different ages according to this study. These results would justify an early start to prophylaxis, at the age of 1 year, but allow a slow escalation in dose and frequency of injections. However, one may argue that treating patients differently, solely on the basis of the number of joint bleeds they have, is disputable in view of the risk of other types of bleedings and the effect on the child's overall quality of life.

Dose and dose interval

Dose and dose interval are important issues when discussing cost-effectiveness of prophylactic treatment.

Table 2. Three groups of children who started prophylactic therapy at different ages but received the same dose and dose interval during the study period ([10], updated at ESPHI (European Society for Paediatric Haematology and Immunology) workshop meeting October 2000)

Age at start of prophylaxis	< 2 years <i>n</i> = 25	2–5 years <i>n</i> = 11	> 5 years <i>n</i> = 19
Joint bleeds before prophylaxis	0–1	6 (median)	> 10 (median)
Orthopaedic score before/after study	0/0 (1)	0/2	4/9
Radiological score before/after study	0/0	0/5	11/17

Table 3. Children (*n* = 55) who started high dose regimen (25–40 IU kg⁻¹) before the age of 5 years [12]

One infusion weekly:	
Prophylaxis started < 3 years	1.1 ± 0.3 bleeds per year
Prophylaxis started 3–5 years	2.1 ± 0.4 bleeds per year
2–3 infusions weekly:	
Prophylaxis started < 3 years	0.8 ± 0.2 bleeds per year
Prophylaxis started 3–5 years	1.2 ± 0.4 bleeds per year

Even in early studies it was noted that scheduling short intervals between infusions was more important than achieving high peak plasma factor concentrations [13,14]. The trough level of FVIII or FIX that is effective in preventing bleeds must be determined individually for each patient. A level > 1% may be useful as a guideline, which experience has shown to yield satisfactory control of the bleeding diathesis in most cases.

Using the computerized pharmacokinetic approach, Berntorp and coworkers [15] used the decay curves of eight patients with haemophilia A to simulate the consumption of FVIII with different dosage schedules the goal being to keep FVIII > 1 IU dL⁻¹. Theoretically, considerable savings of concentrate can be made by giving more frequent infusions, without diminishing the protective effect against bleedings. Continuous infusion seems to be the most cost-effective way of administering factor concentrate but the optimal constant concentration of factor required to prevent bleeds has to be evaluated individually for each patient. To the author's knowledge, continuous infusion of factor concentrates using portable pumps has only been practised on a short-term basis in haemophiliacs, and not for the purpose of prophylaxis but may perhaps be a vision for the future.

Venous access

The start of regular prophylactic treatment at the age of 1–2 years emphasizes the need for uncomplicated venous access. One option in this situation is to begin with one or two injections per week and slowly increase the frequency. Another option is a central venous line, preferably an implantable venous access device such as the Port-A-Cath [16–19]. The main concerns have been the

risk of infections and septicaemia, and a diversity of results have been reported in the literature for the use of the Port-A-Cath in haemophilia patients. When discussing these results one has to evaluate critically if both implanted and external catheters are included, the number of inhibitor patients and HIV-positive patients in different series. In the author's own experience, the Port-A-Cath device may be used in small children with an acceptable frequency and severity of complications, and it allows regular prophylactic or on-demand home treatment of children with haemophilia to be started at an early age [17]. The series comprised 53 children with a Port-A-Cath device. If patients who had inhibitors at the time of implantation (*n* = 11), or developed inhibitors during the study period (*n* = 3), were excluded, the rate of complications was 23% (9/39), corresponding to 0.08 per patient year or 0.23 per 1000 patient days. Many of the children had benefited from the device for a long period of time before a complication occurred (median 18 months, range 1–66). Comparable results were obtained in another recent study (*n* = 41) by Miller and coworkers [19], the overall rate of bacteraemia being 0.14 per 1000 patient days, although the series included patients with inhibitors. In our series no relation was found between the number of punctures for the Port-A-Cath and the frequency of complications (*n* = 53). Although approximately 25% of the patients had complications most parents and doctors considered that they were acceptable and only one parent and three doctors thought that the side-effects were unacceptable.

The use of Port-A-Caths in children were studied in the centres belonging to the European Paediatric Network for Haemophilia Management and it was found that in 3/19 centres > 50% of the boys under the age of 6 had Port-A-Cath while none had the device in 7/19 centres. A few children at some centres used ports after the age of 6 years.

To sum up, in my opinion optimal primary prophylaxis should start at the age of 1–1½ or after the first joint bleed. One should try to use a peripheral vein with 1–2 injections per week and successively increase the frequency depending on the child and the veins.

Depending on the success of using a peripheral vein, the child's activity, social situation and bleeding tendency

a Port-A-Cath may be used which allows a better prophylactic coverage by infusions preferably every second day in haemophilia A and every third day in haemophilia B. However, in all too many parts of the world this regimen must be viewed as a long-range goal in haemophilia care, since in many countries national economic resources are insufficient for regular prophylactic treatment to be feasible at the moment.

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