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Long-term prophylaxis in von Willebrand disease. Experience from Sweden

Pia Petrini
Erik Berntorp
Lennart Stigendal

From the Department of Coagulation Disorders, Karolinska University Hospital Solna, Stockholm, Sweden (PP); Department of Coagulation Disorders, Malmö University Hospital, Malmö, Sweden (EB); , Department of Coagulation Disorders, Sahlgrenska University Hospital, Gothenburg, Sweden (LS).

Correspondence: Pia Petrini, MD Department of Coagulation Disorders, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden. E-mail: pia.petrini@karolinska.se

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, characterized by insufficient or abnormal von Willebrand factor (VWF), a plasma protein essential for primary haemostasis. Patients with VWD are a heterogenous group with respect to clinical manifestations, but the most common bleeding symptoms are mucosal bleedings such as epistaxis and menohrragia.[1,4] Overt haemarthrosis has been considered rare, even in severe VWD, but in recent data from Italy and the US the incidence is in the range of 40% in patients with type 3 VWD.[1,3] Serious or repeated bleeding symptoms cause a significant morbidity in this group of patients and they run the risk of long-term sequelae with respect to joint damage. This paper focuses on long experience of prophylaxis in patients with VWD, involving regular infusions of VWF-containing concentrates.

Design and Methods

Forty-eight patients fulfilling the definition of severe VWD (VWF<8% and FVIII<10%) were identified in Sweden, in a population of nine million. The patients all visited one of the three Haemophilia Centers in Sweden (Gothenburg, Malmö and Stockholm) on a regular basis. 32 of these 48 patients received prophylaxis treatment with at least one infusion of VWF-containing concentrate per week, three received intermittent prophylaxis and 13 received on-demand treatment. 28 of the 35 patients receiving prophylaxis (18 females and 17 males aged from 2-64) were diagnosed with type 3, four were classified with type 2B, two with type 2A and one with type 1. Most of the adult patients have been on a prophylactic regimen for more than ten years. 18 of the 35 patients are under 18 years of age, but even in this group 16 of the patients have received prophylaxis for more than five years. An evaluation was made of data regarding age at the start of prophylaxis, the indication for prophylaxis and complications. Until 1980 the concentrate used was AHF (KABI), but subsequently Haemate (ZLB Behring) has been used.

Results

With respect to the commencement of prophylaxis, 11 patients (31%) started early in childhood, before the age of five, seven patients (20%) started between the ages of 5 and 15, and the remaining 17 patients (49%) began after 15 years of age. As with hemophilia, prophylaxis is started at a younger age today than 20 years ago. The mean age for starting prophylaxis in patients younger than 20 proved to be four (2-7) and for those older than 20 the mean age of commencement was 27 (6-47). The principal indications for prophylaxis were epistaxis or oral cavity bleeds (17 patients), joint bleeds (15 patients) and gastrointestinal bleeds or menorrhagia (3 patients). Review of the indication for prophylaxis versus the age at start (Figure 1) showed that the youngest patients (under five years old) started prophylaxis due to recurrent and severe epistaxis or oral cavity bleeds, often requiring hospital care and blood transfusions. In the adult patient group the primary indications for prophylaxis were haemarthrosis and clinical signs of joint disease. The mean dose of factor concentrate used was 24 (12-48) IU factor VIII per kg body weight and injection. Injection frequency ranged from one to three injections weekly. No significant difference in the mean dose was seen between patients <20 years old and older patients (24 IU vs 23 IU FVIII). Injection frequency was higher in the older patient group (2.7 vs 2.0). The majority of patients who began prophylaxis have remained on this treatment. To date only four of 35 have discontinued prophylaxis. Two females who commenced prophylaxis due to menorrhagia discontinued after 7 and 11 years respectively following a hysterectomy and the menopause. The remaining two started prophylaxis following joint bleeds and stopped after 12 and 13 years respectively.

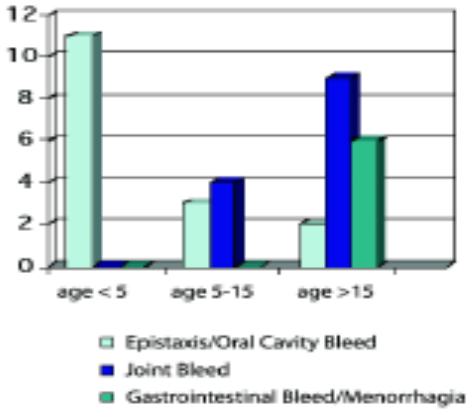

Figure 1. Clinical indication for prophylaxis by age at commencement of therapy.

All patients reported a substantial reduction in severity and frequency of bleeding symptoms. None of the 11 patients who began prophylaxis to prevent severe nose and mouth bleeds had any reports of haemarthrosis or clinical signs of joint disease. In contrast, the group of 17 patients who commenced prophylaxis to prevent progression of joint disease report between one and four joint bleeds per year. Most of them have clinical and radiological signs of artropathy.

Complications

18 of the adult patients were infected with hepatitis C from non-heat-treated product usage. Since the introduction of the pasteurized product, Haemate P, there has been no documented viral transmission.

Three patients developed inhibitors to VWF, two prior to starting prophylaxis and one during this treatment. All subjects had type 3 VWD and were females. Two of them had homozygous mutation at exon 18 and one had a homozygous mutation at exon 28. Two were successfully tolerized and prophylaxis regimens have continued. The youngest patient with inhibitors and allergic symptoms to VWF is treated with recombinant FVIII on demand. There have been no clinical signs of venous thrombosis during prophylaxis.

Case report

The youngest patient on prophylaxis was born in 1999. She was diagnosed with VWD type 3 at the age of six months due to epistaxis and haematomas. At the age of ten months she had a haemarthrosis in the left knee and was treated with Haemate P. During the following year she was hospitalized several times due to severe epistaxis and oral cavity bleedings. Prophylactic treatment with Haemate P 500 IU two to three times a week was started after a Port-A-Cath operation. Pharmacokinetic studies measuring trough and peak values of FVIII and VWF:RCo are performed annually (Table 1). In contrast to patients with Haemophilia A the trough level of factor VIII remains well above basic levels (here 0.21 kie/mL). Since the commencement of this treatment regimen the parents have only reported a few mild mucocutaneous bleeding symptoms per year. These bleedings have been successfully treated with tranexamic acid.

Table 1. Case report: recovery data from a child with b.w. 15 kg. Prophylaxis regimen Haemate 500 IU 2-3 times weekly.

	Baseline	*Peak level (30 min post injection)*	*Trough level (72 hours post injection)*
FVIII kIE/mL	0,01	0,75	0,21
VWF:RCo kIE/mL	< 0,08	1,03	<0,08

Discussion

Prophylactic treatment strategies have, for many years, been considered the optimal treatment for patients with severe haemophilia.[5] Even though the clinical phenotype varies in patients with VWD, the bleeding tendency can be severe, especially in type 3.[4] Epistaxis and oral cavity bleeds can cause a significant morbidity in the youngest patients and the risk of joint damage following hemarthrosis in this patient group may be underestimated.[2,3] FVIII levels may help in predicting which patients are at risk of joint disease, but the exact role of VWF in this type of bleeding is unknown. Although more clinical data and formal studies are needed to establish guidelines for prophylatic treatment strategies in VWD, our data indicates that there is less risk of long-term sequelae in joints if this treatment is initiated at an early age. None of the patients discontinued prophylaxis due to difficulties with frequent intravenous injections. All patients reported a decrease in number and severity of bleeds during prophylaxis and an increased ability to live normal lives.

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