

Prophylaxis in patients with moderate and mild haemophilia: experience from a single centre

Profilaxis en pacientes con formas moderadas-leves de hemofilia: experiencia desde un hospital individual

Carmen Rodríguez-Esteban*, Irene Castaño-Caballero, Raquel Iglesias-Varela, Elsa López-Ansoar, and Manuel Rodríguez-López

Service of Hematology and Hemotherapy, Hospital Universitario Álvaro Cunqueiro, EOXI Vigo, Instituto de Investigación Sanitaria Galicia-SUR, Vigo, Spain

Abstract

Introduction: Prophylaxis in hemophilia as a gold standard of treatment was classically restricted to patients with severe forms. **Objective:** To evaluate the implementation of prophylaxis in patients with moderate and mild hemophilia, addressing its impact on the reduction of bleeding and quality of life. **Material and methods:** Nine patients were included, analyzing retrospective data 12 months before and after starting prophylaxis collected from their electronic medical records. **Results:** It's observed a significant reduction in annualized bleeding rate by 96.78% for hemophilia A and 91.67% for hemophilia B. Concentrates of factors VIII and IX were used with different infusion regimens. Prophylaxis improved hospital independence and decreased joint bleeding, although with a burden associated with treatment. **Conclusions:** The need for early follow-up and adoption of prophylaxis in non-severe patients to prevent arthropathies and improve quality of life is highlighted, in line with international recommendations.

Keywords: Prophylaxis. Non-severe hemophilia. Annualized bleeding rate (ABR). Quality of life.

Resumen

Introducción: La profilaxis en la hemofilia como método preferido de tratamiento se restringía clásicamente a los pacientes con formas graves. **Objetivo:** Evaluar la implementación de profilaxis en pacientes con hemofilia moderada y leve, abordando su impacto en la reducción de sangrados y en calidad de vida. **Material y métodos:** Incluye nueve pacientes, analizando datos retrospectivos 12 meses antes y después de iniciar la profilaxis, datos recogidos de sus historias clínicas electrónicas. **Resultados:** Se observa una reducción significativa de la tasa anualizada de sangrado en un 96,78% para hemofilia A y un 91,67% para hemofilia B. Se emplearon concentrados de factores VIII y IX con distintos regímenes de infusión. La profilaxis mejoró la independencia hospitalaria y disminuyó los sangrados articulares, aunque con una carga asociada al tratamiento. **Conclusiones:** Se destaca la necesidad de un seguimiento temprano y adopción de la profilaxis en pacientes no graves para prevenir artropatías y mejorar la calidad de vida, alineándose con recomendaciones internacionales.

Palabras clave: Profilaxis. Hemofilia no grave. Tasa anualizada de sangrado (TAS). Calidad de vida.

*Correspondence:

Carmen Rodríguez-Esteban

E-mail: carmen.rodriguez.esteban@sergas.es

Date of reception: 07-12-2024

Date of acceptance: 28-07-2025

DOI: 10.24875/RHT.M25000077

Available online: 03-09-2026

Hemost Trombos (Eng). 2026;3(2):51-55

www.revistahemostasiaytrombosis.com

2938-8740 / © 2025 Sociedad Española de Trombosis y Hemostasia (SETH) y Grupo Cooperativo Latinoamericano de Hemostasia y Trombosis (CLAHT). Published by Permanyer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Hemophilia A and B are X-linked recessive disorders caused by deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. Clinically, they are characterized by spontaneous or trauma-related bleeding, the severity of which is associated with the residual plasma activity of the deficient protein.¹ Three severity categories are distinguished: severe (< 1 IU/dL), moderate (1–5 IU/dL), and mild (5–40 IU/dL). Moderate forms are the least common in hemophilia A (HA),² whereas in hemophilia B (HB), the frequency is similar across the different severity categories (33%). According to the latest World Federation of Hemophilia guidelines, prophylaxis should be offered to patients with HA or HB and a severe phenotype. This recommendation includes some patients with moderate hemophilia and a clinically severe phenotype,³ and is supported by the findings of several real-world studies.^{4–6} The latest British clinical practice guidelines⁷ recommend considering prophylaxis for all children with baseline FVIII levels of 1–3 IU/dL. They also recommend offering prophylaxis to any patient with hemophilia who experiences 1 or more spontaneous hemarthroses or who has established joint damage caused by recurrent hemarthroses with ongoing bleeding.

These recommendations are entirely reasonable, considering that “2 or 3 bleeding episodes in the same joint may cause progressive and irreversible damage”⁸ and that “the severity of joint impairment is the main factor affecting the quality of life of our patients.”⁹ We report our center’s experience with the implementation of prophylaxis in a group of patients with moderate or mild hemophilia who agreed to begin this treatment modality and describe its impact on quality of life, both in terms of reduced bleeding and decreased dependence on hospital care.

Objective

To evaluate the impact of prophylaxis with FVIII or FIX concentrates on the health and quality of life of patients with moderate or mild hemophilia A or B treated at a tertiary care center.

Methods

We conducted a retrospective analysis of clinical data from patients with moderate or mild hemophilia who received prophylaxis with factor concentrates. Data were obtained from the electronic health record for the 12 months before and the 12 months after prophylaxis

initiation. The following variables were collected: type of hemophilia; factor level measured using a 1-stage clotting assay; annualized bleeding rate before and after prophylaxis; prophylactic infusion frequency; weekly factor consumption per kilogram of body weight; trough level; presence or absence of arthropathy; and type of prophylaxis, classified as primary, secondary, or tertiary. Quality of life was assessed using the EQ-5D questionnaire (European Quality of Life-5 Dimensions). The analysis was descriptive. Qualitative variables were expressed as absolute values, percentages, and confidence intervals, whereas quantitative variables were expressed as means and SDs.

Results

Nine patients were analyzed: 5 with moderate HA, 4 with moderate HB, and 1 with mild HB. Three patients with HA were children or adolescents. The mean age of the adult patients was 46.8 years (range, 35–73 years). Among all patients at the center with moderate hemophilia and FVIII or FIX levels of 2–5 IU/dL who had previously received on-demand treatment, 75% began prophylaxis with factor concentrates. Six patients were initially included, although the analysis was ultimately conducted in 5 patients with HA. Their mean FVIII activity measured using a clotting assay was 3.4 IU/dL. Mean factor consumption was 105 IU/kg/wk for standard half-life FVIII concentrate, administered 3 times weekly, and 90 IU/kg/wk for extended half-life FVIII concentrate, administered twice weekly. One patient initially began prophylaxis with extended half-life FVIII concentrate once weekly but requested a change to twice-weekly administration because the patient felt safer with the more frequent regimen. Prophylaxis was adjusted to achieve a minimum factor level of 5 IU/dL. The total annualized bleeding rate decreased by 96.78%, from a mean of 6.2 before prophylaxis to 0.2 after prophylaxis. No emergency department visits for bleeding were recorded after prophylaxis initiation. One patient experienced traumatic hemarthrosis of the left ankle that required treatment with 2 additional doses of extended half-life FVIII concentrate, self-administered at home.

A total of 75% of patients with nonsevere HB were receiving prophylaxis: 4 patients with moderate HB, with a mean FIX level of 3.3 IU/dL, and 1 patient with mild HB, with a FIX level of 6 IU/dL. All had established arthropathy of varying severity and at different anatomical sites, most commonly affecting the left ankle. All patients except 1 received prophylaxis with extended half-life FIX concentrate once weekly at a dose of 60 IU/

Table 1. Baseline characteristics, prophylaxis regimen, and changes in annualized bleeding rate in the 9 included patients

Factor level	Preprophylaxis ABR	Preprophylaxis ED visits	Prophylaxis frequency	Factor concentrate	Trough level	Postprophylaxis ABR	Postprophylaxis ED visits	Arthropathy	Type of prophylaxis
3.8 IU/dL	13	13	3 times/wk	SHL, 105 IU/kg/wk	> 5 IU/dL	1	0	No	Primary
3.2 IU/dL	9	9	3 times/wk	SHL, 105 IU/kg/wk	4–5 IU/dL	0	0	No	Primary
3.8 IU/dL	2	1	3 times/wk	SHL, 105 IU/kg/wk	5–6 IU/dL	0	0	No	Primary
4 IU/dL	4	2	2 times/wk	EHL, 90 IU/kg/wk	5–6 IU/dL	0	0	Yes (left ankle)	Tertiary
3.2 IU/dL	3	2	2 times/wk	EHL, 90 IU/kg/wk	4–5 IU/dL	0	0	Yes (right elbow)	Tertiary
3.5 IU/dL	4	4	Once weekly	EHL, 60 IU/kg/wk	5–6 IU/dL	1	0	Yes (left ankle and left elbow)	Tertiary
3 IU/dL	4	4	Once weekly	EHL, 60 IU/kg/wk	5–6 IU/dL	0	0	Yes (left ankle and hip)	Tertiary
6 IU/dL	2	0	Once weekly	EHL, 60 IU/kg/wk	> 6 IU/dL	0	0	Yes (left ankle)	Tertiary
3.5 IU/dL	2	2	Once weekly	SHL, 100 IU/kg/wk	NA	0	0	Yes (knees)	Tertiary

ABR: annualized bleeding rate; ED: emergency department; EHL: extended half-life factor concentrate; NA: not available; OSA: one-stage clotting assay; SHL: standard half-life factor concentrate; wk: week.

kg. The total annualized bleeding rate decreased by 91.67%, from a mean of 3 before prophylaxis to 0.25 after prophylaxis. None of these patients required emergency department care for bleeding. One patient receiving weekly prophylaxis with 100 IU/kg of a standard half-life FIX concentrate experienced traumatic hemarthrosis of the right knee, requiring 3 additional doses of standard half-life FIX concentrate until resolution. Treatment was administered in the Day Hospital at our center (Table 1). Regarding the EQ-5D-5L, the mean index value was 0.8, indicating the presence of some problems in at least 1 dimension but an overall relatively favorable health status within the range of 0.8–1. The reported problems were generally mild to moderate and were mainly related to mobility. The mean visual analog scale score was 90.

Discussion

Several studies have shown that patients with mild or moderate hemophilia may also develop joint lesions and are at risk of requiring orthopedic surgery because of joint bleeding. Therefore, according to current guidelines, identifying candidates for prophylaxis and

implementing this strategy in this patient group are important, particularly among individuals with more severe bleeding phenotypes. A recent publication by the group at *Hospital Universitario La Paz* (Madrid, Spain) evaluated risk factors associated with arthropathy in 85 patients with mild HA.⁶ The investigators analyzed several variables in relation to the presence or absence of joint damage and the severity of arthropathy. Two variables were independently associated with arthropathy: age, with a median of 42 years, and plasma factor activity, with a median of 10.5 IU/dL. The investigators estimated that the risk of arthropathy increased by 7.9% for each additional year of life and decreased by 7.7% for each 1-IU/dL increase in baseline factor activity. Furthermore, once arthropathy developed, its severity could be influenced by the patient's level of physical activity. In our series, the 3 patients receiving primary prophylaxis comprised 2 children and 1 adolescent younger than 18 years who engaged in intensive physical activity. This further supported the implementation of prophylaxis as a treatment strategy. The remaining patients were adults with established joint damage.

The observations reported by the group at *Hospital Universitario La Paz* are consistent with previous findings, including those reported by Wang et al.¹⁰ and Collins,¹¹ who found that the main variable associated with loss of joint range of motion in patients with hemophilia was the plasma factor level, particularly when levels were < 10 IU/dL. The MoHem study,⁵ which evaluated the prevalence of arthropathy in 145 Nordic patients with moderate HA or HB and a median age of 28 years, concluded that current joint health in these patients was generally favorable. However, the investigators identified a subgroup with severe arthropathy. FVIII: C or FIX levels of 3 IU/dL or lower and moderate HA were associated with a more severe bleeding phenotype. The authors therefore suggested primary prophylaxis for patients with FVIII or FIX levels of < 3 IU/dL. Furthermore, they stated that a key factor in joint deterioration was the interval between the first bleeding episode and the age at prophylaxis initiation, with a median interval of 10 years. In addition, when these patients were compared with a Swedish cohort of patients with severe HA receiving prophylaxis, patients with moderate hemophilia reached a Hemophilia Joint Health Score > 10 in half the time required by patients with severe disease. This finding reinforces the observation made by Collins¹¹ regarding the difference in protection against bleeding between, for example, a baseline level of 2 IU/dL in a patient with moderate hemophilia and a trough level of 2% in a patient with severe hemophilia receiving prophylaxis with factor concentrates. In our study, baseline FVIII and FIX levels were slightly higher, at 3.4 and 3.3 IU/dL, respectively. However, 100% of the patients had a history of hemarthrosis, compared with 85% and 73%, respectively, in the MoHem study.

A Dutch study¹² evaluated joint status using magnetic resonance imaging in 51 patients with nonsevere HA, 63% of whom had mild HA and 37% moderate HA, together with the Hemophilia Joint Health Score. The mean FVIII: C level was 10 IU/dL (IQR, 4–16 IU/dL), and the mean age was 43 years. The median Hemophilia Joint Health Score was higher in patients with moderate HA than in those with mild HA, at 7 vs 4. Of note, hemosiderin deposits were found in 14% of joints among patients who had never experienced clinically apparent joint bleeding. This finding may reflect microbleeding or subclinical bleeding and indicates that greater attention should be paid to the joint health of patients with nonsevere hemophilia. Indeed, in the PROBE study,⁴ 82.8% of patients with moderate hemophilia receiving on-demand treatment experienced more than 2–3 bleeding episodes per year.

In our series, prophylaxis was effective in reducing the annualized bleeding rate and the associated disease burden, despite requiring regular infusion of factor concentrates and therefore increasing treatment burden. Currently, no treatment alternatives are available for nonsevere HB beyond intravenous FIX replacement. In HA, however, subcutaneous prophylaxis with emicizumab represents an alternative.¹³ Nevertheless, in patients with moderate HA, defined by FVIII: C levels of 1–5 IU/dL, its use is generally considered in those with a clinically severe bleeding phenotype. In theory, this requirement represents a barrier to the use of emicizumab in primary prophylaxis programs because of the difficulty of predicting the bleeding phenotype using the score proposed by the subcommittees of the International Society on Thrombosis and Haemostasis.¹⁴ This limitation exists despite the favorable findings reported in the HAVEN 6 clinical trial.¹⁵

Álvarez Román et al.¹⁶ suggested that joint damage is not adequately prevented in patients with nonsevere hemophilia. In our series, and overall, patients reported satisfaction with the effect of prophylaxis on their quality of life. Only 1 patient discontinued treatment because of the associated treatment burden. The benefits reported by patients were attributable not only to the reduction in bleeding but also to the decreased need for hospital care and the disappearance of joint pain. Patients were progressively able to increase their physical activity safely because of the additional protection provided by regular factor infusion. Because age and residual plasma factor activity should be considered when estimating the risk of bleeding and, consequently, arthropathy in this patient group, continued follow-up of patients with nonsevere hemophilia in specialized clinics is important.¹⁷ Furthermore, it may be appropriate to consider implementing primary or secondary prophylaxis programs beginning in childhood. Although prophylaxis has not traditionally been considered mandatory for patients with moderate hemophilia, the latest Spanish registry¹⁷ showed that only 26.4% of patients with moderate HA and 24% of those with moderate HB were receiving prophylaxis. Nevertheless, its implementation is likely to become increasingly widespread as further studies confirm the current findings.

Our study has several limitations. First, the small sample size does not allow definitive conclusions to be drawn, particularly regarding the implementation of a treatment strategy associated with high economic costs. Second, it would have been useful to evaluate joint status using the Hemophilia Early Arthropathy Detection With Ultrasound protocol before prophylaxis initiation and again 12 months later. This would have allowed comparison of the findings and objective assessment of

the clinical benefit of prophylaxis beyond the reduction in the annualized bleeding rate. Similarly, quality of life, assessed using the EQ-5D-5L, was evaluated only at the end of the study and not before prophylaxis initiation, which also limits interpretation of this outcome.

Conclusions

In our opinion, prophylaxis should be implemented as the standard of care for patients with moderate or mild hemophilia and a bleeding phenotype to prevent joint complications and improve quality of life. The substantial reduction in the annualized bleeding rate observed among patients with both HA and HB supports this therapeutic approach. In addition to the benefit associated with reducing bleeding frequency, a decrease in the need for hospital visits and an overall improvement in patients' perceptions of their health status were observed.

Although prophylaxis requires a substantial commitment because of the need for regular infusions, its benefits outweigh these barriers, particularly in terms of reduced joint pain and a greater ability to engage safely in physical activity. This series highlights that early implementation of prophylaxis, even in patients with nonsevere hemophilia, may prevent the development of joint complications and reduce the long-term disease burden. Nevertheless, these findings require confirmation in future studies.

Finally, although prophylaxis in nonsevere hemophilia is not currently universally adopted, its use is likely to become more widespread as additional scientific evidence regarding its effectiveness accumulates.

Funding

None declared.

Conflicts of interest

None declared.

Ethical considerations

Protection of human participants and animals. The authors declare that no experiments involving humans or animals were conducted specifically for this study.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely collected, anonymized clinical data; therefore, informed consent

was not required. The relevant ethical recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence tools were used in the preparation of this manuscript.

References

- Seaman CD, Xavier F, Ragni MV. Hemophilia A (Factor VIII Deficiency). *Hematol Oncol Clin North Am.* 2021;35(6):1117-29. DOI: 10.1016/j.hoc.2021.07.006
- Aznar JA, Abad-Franch L, Cortina VR, Marco P; Inherited bleeding disorders group from the Spanish Society of Thrombosis and Haemostasis. The national registry of haemophilia A and B in Spain: results from a census of patients. *Haemophilia.* 2009;15(6):1327-30. doi: 10.1111/j.1365-2516.2009.02101.x
- Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al.; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia.* 2020;26(Suppl 6):1-158. DOI: 10.1111/hae.14046
- Chai-Adisaksopha C, Noone D, Curtis R, Frick N, Nichol MB, Germini F, et al. Non-severe haemophilia: Is it benign? - Insights from the PROBE study. *Haemophilia.* 2021;27 Suppl 1:17-24. <https://doi.org/10.1111/hae.14105>
- Måseide RJ, Berntorp E, Astermark J, Olsson A, Bruzelius M, Frisk T, et al. Joint health and treatment modalities in Nordic patients with moderate haemophilia A and B - The MoHem study. *Haemophilia.* 2020;26(5):891-7. DOI: 10.1111/hae.14114
- De la Corte-Rodríguez H, Rodríguez-Merchan EC, Alvarez-Roman MT, Martín-Salces M, Rivas-Pollmar I, Jiménez-Yuste V. Arthropathy in people with mild haemophilia: exploring risk factors. *Thromb Res.* 2022;211:19-26. <https://doi.org/10.1016/j.thromres.2022.01.010>
- Rayment R, Chalmers E, Forsyth K, Gooding R, Kelly AM, Shapiro S, et al. British Society for Haematology Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. *Br J Haematol.* 2020;190:684-5. doi: 10.1111/bjh.16704
- Gringeri A, Ewenstein B, Reininger A. The burden of haemophilia: is one bleed too many? *Haemophilia.* 2014;20:459-63. <https://doi.org/10.1111/hae.12375>
- Coppola A, Cerbone AM, Mancuso G, Mansueto MF, Mazzini C, Zanon E. Confronting the psychological burden in haemophilia. *Haemophilia.* 2011;17(1):23-7. <https://doi.org/10.1111/j.1365-2516.2010.02280.x>
- Wang M, Recht M, Iyer NN, Cooper DL, Soucie JM. Hemophilia without prophylaxis: assessment of joint range of motion and factor activity. *Res Pract Thromb Haemost.* 2020;4(6):1035-45. DOI: 10.1002/rth2.12347
- Collins PW, Obaji SG, Roberts H, Gorsani D, Rayment R. Clinical phenotype of severe and moderate haemophilia: Who should receive prophylaxis and what is the target through level? *Haemophilia.* 2021;27:192-8. DOI:10.1111/hae.14201
- Zwagemaker AF, Kloosterman FR, Hemker R, Gouw SC, Coppens M, Romano LGR, et al. Join status in patients with non severe Hemophilia A. *J Thromb Haemost.* 2022;20(5):1126-37. <https://doi.org/10.1111/jth.15676>
- Ficha técnica Hemibra® [Internet]. Centro de información online de medicamentos (CIMA) de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Disponible en: https://cima.aemps.es/cima/dochtml/ft/1181271002/FT_1181271002.html
- Mancuso ME, Bidlingmaier C, Mahlangu JN, Carcao M, Tosoletto A, for the Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders. The predictive value of factor VIII/factor IX levels to define the severity of hemophilia: communication from the SSC of ISTH. *J Thromb Haemost.* 2018;16:2106-10. <https://doi.org/10.1111/jth.14257>
- Négrier C, Mahlangu J, Lehle M, Chowdary P, Catalani O, Bernard RJ, et al. Efficacy of emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study. *Lancet Haematol.* 2023;10:e168-77. [https://doi.org/10.1016/S2352-3026\(22\)00377-5](https://doi.org/10.1016/S2352-3026(22)00377-5)
- Álvarez Román MT, de la Corte Rodríguez H, Bonanad Boix S, Mingot-Castellano ME, Fernández Mosteirín N. The factor VIII treatment history of non-severe hemophilia A: COMMENT. Joint damage in adult patients with mild or moderate hemophilia A evaluated with the HEAD-US system. *J Thromb Haemost.* 2021;19:2638-41. <https://doi.org/10.1111/jth.15475>
- Aznar JA, Altisent C, Alvarez Roman MT, Bonanad S, Mingot Castellano E, López MF. Moderate and severe haemophilia in Spain: An epidemiological update. *Haemophilia.* 2018;24(3):e136-e139. doi: 10.1111/hae.13462