

Original article

Impact of personalized pharmacokinetics-guided prophylaxis using standard half-life factor VIII in patients with hemophilia A

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Abstract:

Introduction: Patients with Hemophilia A (HA) are at risk of severe bleeding and joint damage, which can lead to disability. Nonpharmacokinetic (PK)-guided prophylaxis treatment may not be suitable for all patients, as it does not involve personalized prophylaxis tailored to their activity levels. **Objective:** This study aimed to evaluate the clinical impact of PK-guided prophylaxis using standard half-life factor VIII (SHL FVIII) based on activity risk levels in patients with severe phenotype HA. **Materials and methods:** This retrospective and prospective cohort study compared data from the same group of patients receiving prophylactic treatment at Naradhiwasrajanagarindra Hospital between September 2023 and August 2024. Data from 6 months before and 6 months after the implementation of personalized PK-guided prophylaxis, combined with activity risk level design and digital diary application monitoring, were compared. Collected data included the annualized bleeding rate (ABR), annualized joint bleeding rate (AJBR), Hemophilia Joint Health Score (HJHS), Functional Independence Score in Hemophilia (FISH) and weekly consumption of SHL FVIII. **Results:** The study included 12 participants [mean age $\pm$ standard deviation (SD): 16 $\pm$ 6.95 years]. The results showed statistically significant reductions in ABR, AJBR, and HJHS ($p = 0.005$, 0.007 , and 0.002 , respectively). The median [interquartile range (IQR)] FISH score increased from 26.50 (24-28.5) to 28 (26-29.75) ($p = 0.002$), while weekly SHL FVIII consumption did not significantly increase. **Conclusion:** Personalized treatment adjustments using PK data SHL FVIII and digital tools effectively improved treatment outcomes and supported patient activities.

Keywords : ● Hemophilia A ● Personalized ● Pharmacokinetics ● Standard half-life factor VIII

J Hematol Transfus Med. 2025;35:119-27.

Received 31 October 2024 Corrected 4 November 2024 Accepted 28 January 2025

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นิพนธ์ต้นฉบับ

ผลการรักษาแบบป้องกันรายบุคคลโดยใช้เภสัชจลนศาสตร์แฟกเตอร์แปดเข้มข้น เครื่องชีวิตมาตรฐานในผู้ป่วยฮีโมฟีเลีย เอ

อมรา ดือระ

กลุ่มงานกุมารเวชกรรม, โรงพยาบาลนราธิวาสราชนครินทร์

บทคัดย่อ

บทนำ ผู้ป่วยโรคฮีโมฟีเลีย เอ มีความเสี่ยงต่อการเกิดภาวะเลือดออกและบาดเจ็บของข้ออย่างรุนแรง นำไปสู่ภาวะทุพพลภาพ โดยการ
รักษาแบบดั้งเดิมอาจไม่เหมาะสมกับผู้ป่วยทุกราย เนื่องจากการไม่มีการปรับการรักษาแบบป้องกันตามกิจกรรมรายบุคคล **วัตถุประสงค์**
เพื่อประเมินผลลัพธ์ของการปรับการรักษาแบบป้องกันตามค่าเภสัชจลนศาสตร์ (PK) โดยใช้แฟกเตอร์แปดเข้มข้นเครื่องชีวิตมาตรฐาน
ตามกิจกรรมรายบุคคลของผู้ป่วยฮีโมฟีเลีย เอ ชนิดรุนแรง **วัสดุและวิธีการ** ศึกษาติดตามย้อนหลังและไปข้างหน้า เปรียบเทียบข้อมูล
ผู้ป่วยในกลุ่มเดียวกันและได้รับการรักษาแบบป้องกัน ณ โรงพยาบาลนราธิวาสราชนครินทร์ (กันยายน 2566 ถึง สิงหาคม 2567) โดย
เปรียบเทียบข้อมูลในช่วง 6 เดือนก่อนและ 6 เดือนหลังจากการใช้ค่า PK รายบุคคล มาปรับการรักษาและติดตามผลจากแบบบันทึก
ดิจิทัล ข้อมูลที่เก็บรวบรวมได้แก่ อัตราการเกิดเลือดออกต่อปี (ABR) อัตราการเกิดเลือดออกในข้อต่อปี (AJBR) คะแนนสภาพข้อ
(HJHS) คะแนนประเมินความสามารถในการทำกิจกรรมประจำวัน (FISH) และแฟกเตอร์แปดเข้มข้นเครื่องชีวิตมาตรฐานต่อสปีดาห์
ผลการศึกษา ผู้ป่วยจำนวน 12 ราย (มีอายุ mean±SD เท่ากับ 16±6.95 ปี) พบว่า ABR, AJBR และ HJHS ลดลงอย่างมีนัย
สำคัญทางสถิติ ($p = 0.005, 0.007$ และ 0.002 ตามลำดับ) คะแนน median (IQR) ของ FISH เพิ่มขึ้นจาก 26.50 (24-28.5) เป็น
28 (26-29.75) ($p = 0.002$) ขณะที่การใช้ แฟกเตอร์แปดเข้มข้นเครื่องชีวิตมาตรฐาน ต่อสปีดาห์ไม่ได้เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ
สรุป การปรับการรักษาแบบรายบุคคลด้วยการใช้ค่า PK และเครื่องมือดิจิทัลช่วยปรับปรุงผลการรักษาและสนับสนุนกิจกรรมของผู้
ป่วยได้อย่างมีประสิทธิภาพ

คำสำคัญ : ● ฮีโมฟีเลียเอ ● รายบุคคล ● เภสัชจลนศาสตร์ ● แฟกเตอร์แปดเข้มข้นเครื่องชีวิตมาตรฐาน

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2568;35:119-28.

Introduction

Hemophilia A is a hereditary bleeding disorder characterized by a deficiency of clotting factor VIII (FVIII), resulting in spontaneous or trauma-induced bleeding. Prophylactic treatment with FVIII is the standard of care for hemophilia A, aiming to prevent bleeding episodes, protect joint health and improve the quality of life.¹ However, fixed-dose regimens often fail to account for interpatient variability in pharmacokinetics (PK), which can lead to under- or overtreatment.²

Personalized PK-guided prophylaxis has emerged as a promising approach to optimize FVIII dosing by tailoring treatment, based on individual PK parameters, including half-life, clearance and volume of distribution.³⁻⁶ Advances in technology, such as PK modeling software, have facilitated the implementation of personalized prophylaxis in clinical practice. Digital tools allow clinicians to calculate individualized FVIII dosing regimens with minimal blood sampling, enabling effective and practical PK assessments.⁷

In addition, mobile applications have been developed to enhance patient engagement and treatment monitoring. These applications provide tools for tracking bleeding episodes, recording treatment adherence, and visualizing progress in real time, thereby supporting a patient-centered approach to care.⁸⁻¹¹

This study aims to evaluate the impact of personalized PK-guided prophylaxis using standard half-life (SHL) FVIII in patients with hemophilia A. By population PK for dose optimization and digital tool application for patient monitoring, we aim to assess the effectiveness of this approach in reducing bleeding episodes and improving clinical outcomes.

Materials and methods

Study population

This study was a retrospective and prospective cohort study at a single center, Naradhiwasrajanagarindra Hospital, Thailand, from September 2023 to August 2024. Because the disease is rare and the sample size was

not pre-calculated, a convenience sampling method was used. We recruited patients aged 4 to 30 years with severe hemophilia A (FVIII: c < 1 IU/dL) or moderate hemophilia A (FVIII: c 1-5 IU/dL) with severe bleeding phenotype¹ [annualized bleed rate (ABR) $\geq$ 5 bleeds/year or annualized joint bleed rate (AJBR) $\geq$ 3 joint bleeds/year]. Eligible patients must have received SHL FVIII concentrate prophylaxis for at least six months prior to the study. Inhibitor testing, performed within six months before the study, must have yielded negative results. Patients were excluded if they had bleeding disorders unrelated to Hemophilia A or a platelet count of less than 100,000/mm³. The study protocol was ethically approved by the Ethics Committee of Naradhiwasrajanagarindra Hospital (No. 009/2567). All patient participants and their parents provided informed consent.

PK-guided prophylaxis treatment and activity risk level intervention

All participants underwent a detailed bleeding history assessment, physical examination and evaluation of joint function. Each received SHL FVIII low-dose prophylaxis (10-15 IU/kg) or intermediate dose prophylaxis (15-20 IU/kg) once to twice weekly. The study comprised two phases, each lasting six months: a retrospective phase (prePK-guided) and a prospective phase (postPK-guided). During the prospective phases, personalized prophylaxis was guided by individual PK profiles generated using population PK-based software to personalize the dosing of SHL FVIII for patients with hemophilia A. Blood samples were collected at 3 and 24 hours post-infusion without a washout period to reflect real-life clinical conditions. The software enabled individualized dose adjustments based on activity levels and target trough thresholds, optimizing bleed prevention and factor utilization.¹²⁻¹⁵

Interventions were tailored based on patient needs and activity levels. PK-guided adjustments were made to either increase the dose, increase the dosing interval or decrease the dosing interval to achieve a trough level of $\geq$ 3% for low-risk activities (e.g., walking, light household tasks) and $\geq$ 5% for higher-risk activities (e.g., badminton, sepak takraw, running, gardening).¹⁶

By using PK-guided prophylaxis, the treatment approach was adjusted, and activity planning was coordinated by communicating the time of peak drug levels and avoiding activities when drug levels were at trough levels.¹³ Individual patients were consulted to design activity plans, including the specific timing and duration for activities. The dosage and frequency were then adjusted accordingly. In some cases, the dosing interval was reduced if the activity level was not sufficiently high.

When breakthrough bleeding occurred, it was treated with on-demand SHL FVIII at a dose of 20-40 IU/kg for mild bleeds and 30-50 IU/kg for moderate to severe bleeds every 12 hours. All bleeding episodes were documented using a digital diary application, noting the type, severity and trigger. Patients experiencing frequent bleeds (> 1 per month) underwent PK reassessment, and their prophylaxis regimen was adjusted to maintain higher trough levels. Bleeding data were reviewed regularly during follow-up visits to ensure effective prophylaxis and prevent recurrence.

Study outcome measurement

Data collection utilized a digital diary application to document factor administration, bleeding episodes, locations of bleeding and accompanying images in cases of breakthrough bleeding. Treating physicians were able to provide real-time guidance and treatment based on this data.⁸⁻¹¹ The study included a retrospective review of data from six months prior to the study and a prospective assessment during the six months of the study. The outcomes included the ABR and AJBR, which were calculated and extrapolated to reflect a 12-month period. The Hemophilia Joint Health Score (HJHS)¹⁷ and the Functional Independence Score in Hemophilia (FISH)¹⁸ were evaluated by rehabilitation physicians and physical therapists. Joint outcomes were assessed based on the presence and number of target joints (≥ 3 spontaneous bleeds occurring within a consecutive six-month period). FVIII consumption was recorded based on regular doses and breakthrough bleeding doses.

The primary outcomes were the bleeding rates, ABR and AJBR. Other hemophilia-related clinical outcomes included HJSH and FISH. The secondary outcome was the change in SHL FVIII consumption, recorded in IU/kg/week.

Statistical analysis

Data were presented as percentages, frequencies, and median with ranges or interquartile ranges (IQR) for non-normally distributed data or means with standard deviations (SD) for normally distributed data. For comparative analyses, a paired t-test was employed; if the data did not exhibit a normal distribution, the Wilcoxon signed-rank test was used. A statistical significance level of $p < 0.05$ was established. Data analysis was conducted using IBM SPSS Statistics software version 26.

Results

Patients' characteristics

The study included datasets from 12 patients. The baseline characteristics of these patients are presented in Table 1. The mean (SD) age of the patients was 16 (6.95) years, with a mean (SD) body weight of 44.18 (23.03) kg and a mean (SD) body mass index (BMI) of 19.11 (5.15). All patients exhibited a severe HA phenotype and received regular SHL FVIII prophylaxis. The mean dosage administered was 14.31 (4.37) IU/kg/dose. Among the patients, seven used secondary prophylaxis, whereas five patients used tertiary prophylaxis.

Regarding target joints, five patients had one target joint (41.67%), four patients had two target joints (33.33%), and three patients had three target joints (25%).

PK data were collected for both pre- and post-PK-guided treatment. In the six months before the study (pre-PK-guided), 11 patients received SHL FVIII concentrates twice weekly, and one patient received it once weekly. Nine patients received a low dose of SHL FVIII concentrates, whereas three patients received an intermediate dose. Personalized PK parameters and post-PK-guided prophylaxis regimens were communicated to patients based on the time above target FVIII trough levels of 3 IU/dL (hours) and 5 IU/dL (hours) as shown in Table 2.

Table 1 Patient characteristics at baseline (n = 12)

Characteristics	Statistical values
Age in years, mean (<i>SD</i>)	16±6.95
Weight (kg), mean (<i>SD</i>)	44.18±23.03
BMI (kg/m ²), mean (<i>SD</i>)	19.11±5.15
Number of target joint (s), n (%)	
- 1 joint	5 (41.67)
- 2 joints	4 (33.33)
- 3 joints	3 (25.00)
ABR Pre-study	
- Median (<i>IQR</i>)	7 (4-19)*
AJBR Pre-study	
- Median (<i>IQR</i>)	4 (0.5-11)*
HJHS Pre-study	
- Median (<i>IQR</i>)	6 (5-12.75)*
FISH Pre-study	
- Median (<i>IQR</i>)	26.5 (24-28.5)*
Factor VIII consumption(IU/kg/week)	
- Median (<i>IQR</i>)	29.94 (27.90-42.74)*

Note: BMI, Body mass index; ABR, Annualized bleed rate; AJBR, Annualized joint bleed rate; HJHS, Hemophilia Joint Health Score; FISH, Functional Independence Score in Hemophilia; IQR, Interquartile range; SD, Standard deviation; IU, International unit; kg, Kilogram

*The median (*IQR*) is presented as the data is non-normally distributed.

Breakthrough bleeding

The number of bleeding episodes among patients pre- and post-PK-guided, categorized by activity risk level, is presented. All patients followed a time-based activity plan. Six patients selected mild activity, with a target trough level of ≥ 3 IU/dL, while another six patients chose higher-risk activities with a target trough level of ≥ 5 IU/dL. The number of bleeding episodes pre- and post-PK-guided is shown in Table 3.

Clinical outcomes

The clinical outcomes following treatment adjustments, based on lifestyle activities and joint conditions, along with communication regarding PK-guided prophylaxis, were monitored through the ABR and AJBR through the digital diary tool. Both the ABR and AJBR showed significant reductions, as presented in Table 4. The median (*IQR*) ABR decreased from 7 (4-19) bleeds/year to 2 (0-5.5) bleeds/year ($p = 0.005$), and the AJBR

decreased from 4 (0.5-11) bleeds/year to 0 (0-3) bleeds/year ($p = 0.007$). Both median ABR and AJBR significantly decreased, with the ability to achieve zero joint bleeds.

Evaluations of joint status using the HJHS and the FISH revealed significant improvement. The median (*IQR*) HJHS improved from 6 (5-12.75) to 4 (2-10) ($p = 0.002$). The median (*IQR*) FISH also increased from 26.50 (24-28.5) to 28 (26-29.75) ($p = 0.002$) as shown in Table 4.

Factor consumption

The consumption of SHL FVIII concentrate was monitored, comparing usage over the six months before the study and the six months following its implementation using the digital diary tool. The administration of FVIII concentrate according to both pre-PK guided and post PK-guided prophylaxis programs for daily activities, as well as treatment during breakthrough bleeding, showed no statistically significant differences as shown in Table 5.

Table 2 Pharmacokinetics data

Patient number	Age (year)	BW (kg)	Baseline FVIII level (%)	Half-life (hour)	SHL FVIII		Pre/Post PK-guided Time above Target FVIII Trough level 3,5 IU/dL (hour)	
					dose (IU Interval/dose(IU/kg/dose))	Post PK-guided/ IUInterval /IU/kg/dose	3 IU/dL	5 IU/dL
1	4	12.5	0.4	8.2	250 x 1 weekly/20	No change/20	27/27	21/21
2	10	22	< 1	7.8	500 x 2 weekly/22.72	500 x (↓) 1 weekly/22.72	27/27	21/21
3	11	22.4	0.9	9.8	250 x 2 weekly/11.16	(↑) 500 x 2 weekly/22.32	24/34	17/27
4	12	38	< 1	8	500 x 2 weekly/13.16	500 x (↓) 1 weekly/13.16	20/20	15/15
5	12	25	2.5	9	500 x 2 weekly/20	No change/20	43/43	29/29
6	15	37.5	2	10.2	500 x 2 weekly/13.33	No change/13.33	43/43	27/27
7	15	35	2.2	7.4	500x 2 weekly/14.29	500 x (↑) 3 weekly/14.29	31/31	20/20
8	19	53	2.0	11.2	500 x 2 weekly/9.43	(↑) 750 x 2 weekly/14.15	43/49	25/31
9	20	80	0.17	9.5	750 x 2 weekly/9.38	(↑) 1000 x 2 weekly/12.50	20/22	13/16
10	22	70	< 1	7.6	750 x 2 weekly/10.71	(↑) 1000 x (↑)3 weekly/14.29	15/18	10/13
11	22	56.7	2.1	8.6	750 x 2 weekly/13.23	(↑) 1000 x 2 weekly/17.64	35/39	22/25
12	30	78	< 1	8.4	1000 x 2 weekly/12.82	1000 x (↓) 1 weekly/12.82	20/20	15/15

Note: BW, Body weight; FVIII, Factor VIII; SHL, Standard Half-life; IU, International unit; PK, Pharmacokinetic; kg, Kilogram; (↑), Decrease; (↓), Increase

Table 3 Numbers of breakthrough bleeding activity risk pre-PK-guided and post PK-guided prophylaxis (time based activity plan and dose/interval adjustment)

Patient number	Activity risk level	Target trough level (%)	Number of breakthrough bleeding	
			Pre PK-guided	Post PK-guided
1, 2, 4, 5, 6, 12	Mild activity (walking, light household task)	≥ 3	5, 2, 2, 2, 6, 4	0, 0, 0, 0, 0, 1
3, 7, 8, 9, 10, 11	Higher risk activity (badminton, sepak takraw, running, gardening)	≥ 5	4, 2, 6, 4, 6, 5	2, 0, 0, 1, 1, 2

Note: PK, Pharmacokinetic

Table 4 Summary of clinical outcomes for hemophilia A patients receiving personalized PK-guided prophylaxis

Outcome parameters	Statistics value, median (IQR)		p-value
	Pre PK-guided	Post PK-guided	
ABR All patients (n = 12)	7 (4-19)	2 (0-5.5)	0.005
AJBR All patients (n = 12)	4 (0.5-11)	0 (0-3)	0.007
HJHS All patients (n = 12)	6 (5-12.75)	4 (2-10)	0.002
FISH All patients (n = 12)	26.5 (24-28.5)	28 (26-29.75)	0.002

Note: ABR, Annualized bleed rate; AJBR, Annualized joint bleed rate; HJHS, Hemophilia Joint Health Score; FISH, Functional Independence Score in Hemophilia; IQR, Interquartile range

Table 5 Factor VIII consumption (all patients n = 12) regular prophylaxis breakthrough bleeding and total pre- and post-PK-guided

Factor consumption (IU/kg/week)	Statistics value, median (IQR)		p-value
	Pre PK-guided	Post PK-guided	
Regular prophylaxis Doses	25.98 (20.36-28.09)	27.48 (20.68-42.15)	0.515
Breakthrough Bleeding Doses	5.14 (2.95-8.65)	0 (0-0.58)	0.002
Total Doses	29.94 (27.90-42.74)	27.48 (20.68-43.01)	0.530

Note: IU, International unit; PK, Pharmacokinetic; kg, Kilogram

Discussion

The results of this study demonstrate that personalized PK-guided dosing for patients with hemophilia A, combined with activity-based dosing adjustments, significantly improved bleeding control, joint health and functional scores. Our findings support the use of trough-level monitoring to optimize FVIII prophylaxis, particularly in patients engaging in mild to higher-risk activities.¹⁶ By adjusting doses based on individual PK profiles and aligning physical activities with optimal trough levels, we were able to maintain therapeutic

levels and prevent bleeding episodes, including breakthrough bleeds.

A significant reduction in both ABR and AJBR was observed, suggesting that PK-guided dosing can effectively reduce the risk of bleeding while improving overall joint health. Specifically, patients who followed trough-level recommendations during physical activity had fewer breakthrough bleeds and improved joint scores, as assessed by the FISH and HJHS systems. The reduction in ABR and AJBR observed in this cohort is consistent with previous studies that have shown a

positive correlation between tailored prophylaxis and bleeding control in patients with hemophilia A.¹⁹⁻²⁰

Factor consumption remained stable, with no significant difference observed between the baseline and post-study periods, indicating that PK-guided dosing can maintain adequate protection while minimizing unnecessary factor use.²⁰ Interestingly, patients who adhered to the activity-based dosing adjustments experienced reduced breakthrough bleeding and were able to maintain therapeutic trough levels during key activity periods. This suggests that dose optimization, rather than increased factor consumption, is a more effective approach to managing patients with hemophilia A during physically demanding activities.

Patient adherence to activity-based dosing schedules and trough-level management was crucial in achieving these positive outcomes. Digital diaries used to monitor activity levels and bleeding events were an effective tool for enhancing patient engagement and ensuring timely adjustment to dosing regimens.⁹⁻¹¹ This highlights the importance of patient education and regular follow-up in optimizing bleeding prevention and maintaining joint health. However, adherence to trough-level recommendations was not universal, and a few patients still experienced breakthrough bleeds. This could be attributed to a combination of noncompliance and fluctuations in individual PK profiles that may require further study to refine dosing strategies.

Limitations encountered in this study include a small sample size and its conduct at a single hospital under the Ministry of Public Health. Additionally, only one type of SHL FVIII concentrate was used, and dosing began with low doses, with some patients receiving intermediate doses to align with budget constraints and medication suitability.

Conclusion

This study demonstrates the feasibility and effectiveness of a PK-guided prophylactic approach supported by a digital diary tool in optimizing outcomes for

patients with hemophilia A. By tailoring factor dosing to patient activities and PK profiles, we achieved significant reductions in ABR and AJBR, improved joint health and functional scores without significantly increasing factor consumption.

The integration of digital tools for dose adjustment and monitoring highlights the potential for digital innovation to revolutionize hemophilia care. These findings support the use of individualized, data-driven approaches in rare disease management and underscore the importance of patient engagement in achieving optimal outcomes. Further studies are warranted to expand on these results and explore the application of this model in larger cohorts and diverse clinical settings.

Acknowledgments

We would like to thank the patients and their parents for their cooperation in this study, as well as the personnel involved, including medical technologists, rehabilitation physicians, physical therapists and the administrators of the digital diary tool who supported this research.

Conflicts of Interest

This study received support in the form of Factor VIII assay kits from Med-One.

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