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ORIGINAL ARTICLE

Individualised prophylaxis based on personalised target trough FVIII level optimised clinical outcomes in paediatric patients with severe haemophilia A

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Abstract

Introduction: As standard care of severe haemophilia A (SHA), prophylaxis should be individualised.

Aim: This study aimed to investigate the effectiveness of this new-proposed individualised prophylaxis protocol.

Methods: Boys with SHA were enrolled and followed a PK-guided, trough-level escalating protocol of prophylaxis after a six-month observational period. In the next 2 years, clinical assessments including joint bleeds, ultrasound (US) scores and Haemophilia Joint Health Score (HJHS) in both sides of ankles, knees and elbows were conducted every 6 months as a scoring system, which determined whether the trough level's escalation. Adjustment of dosing regimen was based on WAPPS-Hemo.

Results: Fifty-eight SHA boys were finally analysed. Their age and bodyweight were 5.3(2.8,6.9) years and 21.5(16,25) kg. During the study, 47 escalations were conducted. At study exit, the patient number and proportion of different trough level groups were: < 1 IU/dl, 17.2% (10/58); 1–3 IU/dl, 53.5% (31/58); 3–5 IU/dl, 15.5% (9/58); > 5 IU/dl, 13.8% (8/58). Significantly reduced annualised bleeding rate [4(0,8) to 0(0,2), $p < .0001$] and annualised joint bleeding rate [2(0,4) to 0(0,.25), $p < .0001$] was observed at study exit as well as the continuous trend of increased zero bleeding proportion (ZBP) (27.6%–69.0%) and zero joint bleeding proportion (46.5%–81.3%). Besides, 85% (6/7) of the target joints vanished. Statistical improvements of US scores ($p = .04$) and HJHS ($p = .02$) were also reported at study exit.

Conclusion: Our results showed the effectiveness of our protocol based on individualised target trough level and emphasise the importance of personalised prophylaxis.

KEYWORDS
bleeds, Factor VIII, haemophilia A, paediatrics, pharmacokinetics, prophylaxis

1 | INTRODUCTION

Currently, regular prophylactic infusions of exogenous FVIII to prevent bleeding is the standard of care for haemophilia A patients with severe bleeding phenotype due to its long-term proved safety and efficacy.[1,2] Due to the inter-individual variability in FVIII metabolism, trough FVIII level is the most important indicator for prophylaxis in SHA.[3,4] The initial prophylactic protocol was designed to keep patients' trough FVIII level above 1 IU/dl, converting the patients' severe haemophilia phenotype to moderate.[5] Collins et al. showed that the number of break-through bleeds increased proportionately with the average time spent with FVIII level under 1 IU/dl in prophylaxis.[6] Modelling by Chowdary et al. suggested that every escalation of 1 IU/dl in trough level could bring an additional 2% of patients having zero bleeds.[7] After decades of exploration, the current World Federal of Haemophilia (WFH) also recommends a higher target trough level of at least 3 IU/dl to replace the traditional 1 IU/dl.[1]

For a specific individual, higher trough level always means better clinical outcomes. However, the minimum necessary target trough level required to achieve zero bleed and optimised joint protection varies between different patients, due to the inter-individual variability of bleeding phenotype and joint vulnerability.[4] Therefore, the optimal prophylaxis regimen should be an individualised treatment based on bleeding phenotype, joint status and clotting factor availability/affordability.[1,8] Such individualised prophylaxis strategy based on personalised target trough FVIII level would be a more cost-effective choice, and is particularly important for resource-restricted developing countries. Thus, we proposed an individualised prophylaxis protocol using a PK-guided, trough level escalating design which might optimise clinical outcomes by gradually finding the ideal individualised target level.

2 | MATERIALS AND METHODS

2.1 | Ethics approval

The study was approved by the Ethics Committee of the Beijing Children Hospital and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each enrolled patient and/or their legal guardians. The study was registered in ClinicalTrial.gov as NCT03622476. This manuscript is the final report of this study.

2.2 | Study design

This a 2.5-year prospective, interventional, singe-centre study with Figure 1 showing the study design. At enrollment, all the eligible participants had PK assessment and joint evaluations as depicted in Table 1. The patients were then followed every 6 months until study exit. The first 6-month was considered as observation period for the individual patients to obtain the baseline evaluation results while remaining on their original dosing regimen. In the next 24 months (individualised prophylaxis period), the patients were evaluated at each follow-up using a scoring scale (Table 1) based on joint evaluations to determine if the prophylactic regimen needed escalation. If prophylaxis was judged to be sufficient, the dosing regimen would remain unchanged in the

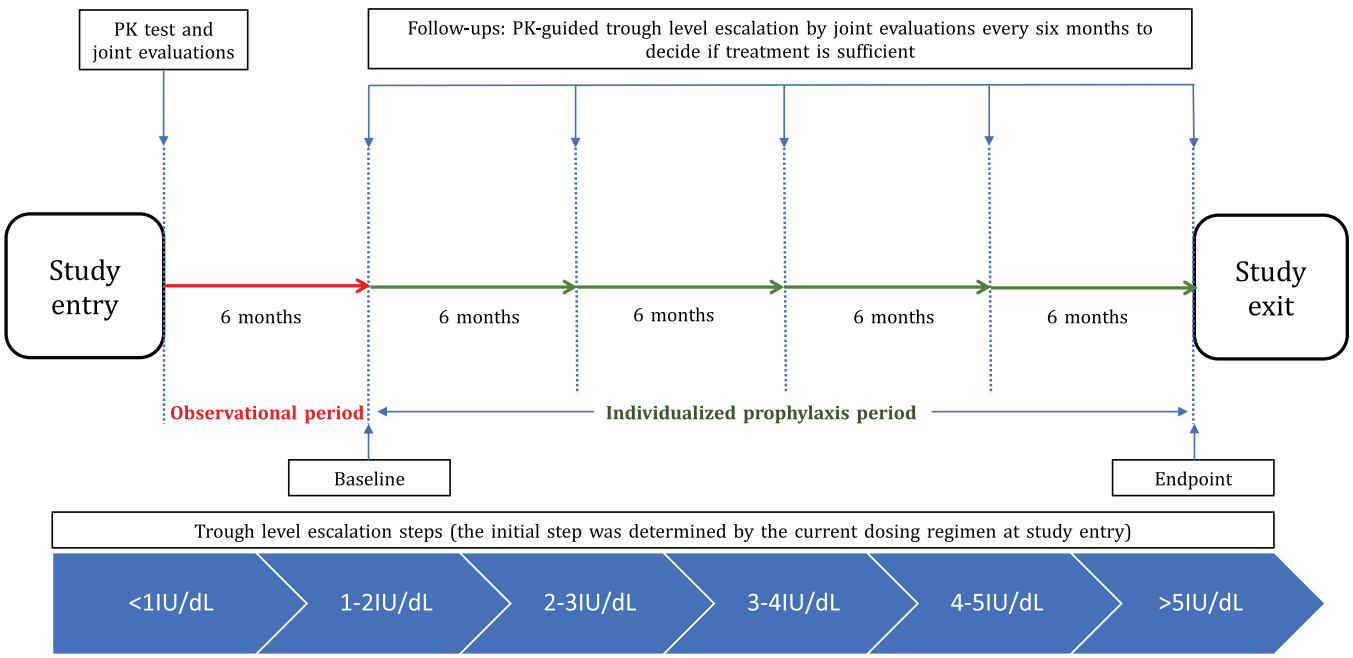

FIGURE 1 Study design

TABLE 1 Joint evaluations and scoring system

	Index joint assessment	Frequency	Description	Score
Bleeding (1–18 years)	Bleeding	Every 6 months	No bleeding	0
			1 index joint bleed	+1
			≥2 bleeds in any single index joint	+2
Clinical imaging (1–18 years)	Ultrasound	Every 6 months	No change or improved	0
			Ultrasound scores increment = 1 or new significant hematoma/joint hematoma/ hemosiderosis	+1
			Ultrasound scores increment≥2 or new severe hematoma/joint hematoma/ hemosiderosis	+2
Joint function (4–18 years)	HJHS	Every 6 months	No change or improved	0
			Change of swelling score on HJHS (not considered to be related to an acute bleed)	+2

Abbreviation: HJHS, haemophilia joint health score.
The prophylaxis regimen would be defined as 'sufficient' if the total score was <2 scores. Total scored ≥2 would be considered as 'insufficient', and the patient will escalate to the next higher trough level with a new dosing regimen calculated based on the individual PK profiles.

next 6-month period. If the standard of escalation was met, each escalation will involve a stepwise increase in the trough level for which the dose/frequency adjustment would be based on their individual PK profiles for the FVIII product used. The stepwise escalations of trough level were: < 1 IU/dl, 1–2 IU/dl, 2–3 IU/dl, 3–4 IU/dl, 4–5 IU/dl and > 5 IU/dl. The initial step was determined according to their current trough level calculated by individualised PK profiles and dosing regimen instead of simply starting from < 1 IU/dl. The adjustment of dose and frequency is flexible as long as the updated trough level fall into the corresponding range.

2.3 | Escalation standard and scoring scales

The joint evaluations included the assessment of the *six index joints* (both sides of ankles, knees and elbows) for joint bleeds, ultrasound (US) score and haemophilia joint health score (HJHS) using a scoring scale depicted in Table 1. The prophylactic regimen would be defined as 'sufficient' requiring no escalation if the total score was <2. If the score was ≥2, the prophylactic regimen would be considered insufficient and the patient regimen would be escalated to fall into the next higher trough FVIII level range.

2.4 | Patients

The paediatric patients with severe haemophilia A were enrolled at the Beijing Children Hospital from June 2018 to 2019. The inclusion criteria were (1) age <18 years; (2) severe haemophilia A (FVIII activity < 1 IU/dl); (3) already on prophylaxis taking plasma derived or recombinant FVIII concentrates; (4) already treated for more than 50 exposure days. The exclusion criteria were (1) current FVIII inhibitor [>.6BU (Bethesda unit)/ml, confirmed by two separate tests]; (2) other bleeding disorders.

2.5 | Blood samples and Laboratory assay

After a washout period of 72 h, each patient received a single FVIII infusion of 50 IU/kg for PK study. A multi-point blood sampling strategy was used (pre-dose, as well as 1, 9, 24, and 48 h post-infusion). For each patient, FVIII activity level and FVIII inhibitor were determined. The one-stage activated partial thromboplastin time-based assay was used to measure FVIII activity, with HemosIL® FVIII deficient plasma (Instrumentation Laboratory, Bedford, MA, USA).

2.6 | PK evaluation

Pharmacokinetic analysis was performed by Web-Accessible Population Pharmacokinetic System (WAPPS-Hemo).[9] The patient's trough level based on his current FVIII dose and dosing frequency was calculated using the 'Clinical Calculator' function in WAPPS-Hemo.

2.7 | Bleeding rates

The overall bleeds and joint bleeds were obtained through their routine bleeding records and verified at each follow-up visits for calculation of the various annualised bleeding rates including annualised bleeding rate (ABR), annualised joint bleeding rate (AJBR). Besides, zero bleeding proportion (ZBP), zero spontaneous bleeding proportion (ZBP), zero joint bleeding proportion (ZJBP) and zero spontaneous joint bleeding proportion (ZSJBP) were also calculated in different

trough level groups and during different periods. Since the study (2.5 years) was divided into five 6-months, the bleeding rates of each specific 6-month was calculated according to the bleeding records of the corresponding 6-month.

2.8 | Joint evaluations

2.8.1 | Target joint

An index joint with ≥3 spontaneous bleeds in a consecutive six-month period was defined as a target joint.[10] Resolution of target joint bleeding was defined as ≤2 bleeds into the index joint within a consecutive twelve-month period.

2.8.2 | Ultrasound (US) evaluation

The six index joints were evaluated by Ultrasound at study entry and during the each 6 monthly follow-up as previously described by Zhang et al.[11] The scoring item included the evaluations of effusion/bleeding, synovial change, hemosiderin deposition and bone/cartilage change. The scores ranged up to 14 for each index joint. The US evaluations were performed by two experienced radiologists (Ningning and Aihua) and differences in scores were adjudicated by consensus.

2.8.3 | Haemophilia Joint Health Score (HJHS)

The musculoskeletal evaluation of each patients' joints was conducted by experienced physiotherapist for all the boys above 4 years age. The version 2.1 scoring scale was used.[12] The HJHS of all our patients were performed by Yan Wang alone.

2.9 | Quality of life and FVIII consumption

Patients' quality of life was estimated by the Canadian Haemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT, Chinese Version 2.1) as previously described.[13] Both the main sheet and the socio-economic context (SEC) sheet were completed. The FVIII consumption was calculated through the dose and frequency of their routine prophylaxis.

2.10 | Statistical analysis

The statistical analysis and the figure generation were performed using GraphPad Prism for Mac (Version 9.1). Data were reported as median (upper quartile, lower quartile) with range. Patient number or escalation number were depicted as number with proportion. Paired Wilcoxon tests were used to evaluate the difference of annualised bleeding rates, US scores and HJHS scores. Fisher's tests were utilised to compare the zero bleeding proportions. The comparison of these indicators was conducted between baseline period and other 6-months in individualised prophylaxis period as well as between each 6-month and its previous 6-month. p values $< .05$ indicates a statistically significant difference.

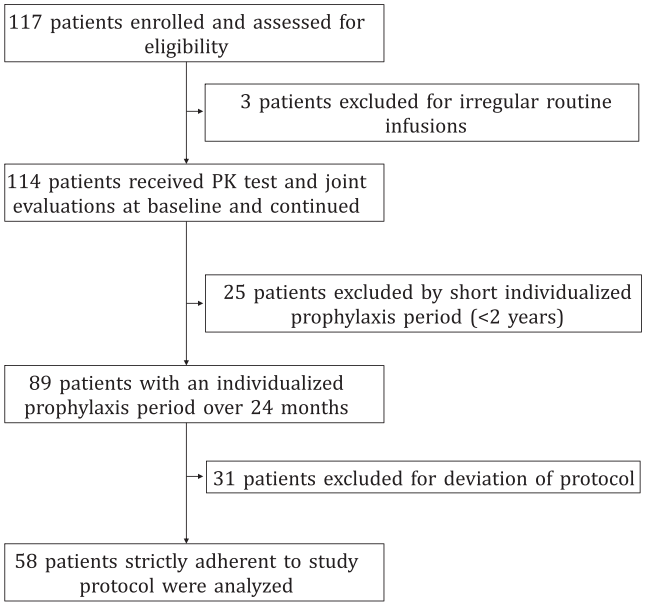

FIGURE 2 Patients' enrollment and exclusion

3 | RESULT

3.1 | Participants

At study entry, 117 patients were enrolled. During the study period, three patients were excluded due to poor adherence to prophylaxis. Of the remaining 114 patients, 89 individuals had an individualised prophylaxis period over 24 months. Among these 89 patients, 58 who strictly followed the protocol without any deviation during the study period were analyzed for clinical outcomes Figure 2.

The baseline characteristics of the 58 patients analyzed were shown in Table 2. Their median age was 5.3 (3.8, 6.9) years. At baseline, the median initial FVIII dose of each infusion was 21.7 (16.1, 27.9) IU/kg with a wide range of 5.3–53.3 IU/kg. Their main dosing frequency were every other day [qod, $N = 19$ (32.8%)], twice per week [biw, $N = 14$ (24.1%)] and three times per week [tiw, $N = 15$ (25.9%)]. The dosing intervals were 2.34 (2.0, 3.5) days ranged from daily to weekly. At baseline, 34 (58.6%) patients had a trough level below 1 IU/dl and nobody had a trough level > 5 IU/dl. Six patients had seven target joints according to their bleed records, that included two elbows, one knee and four ankles.

3.2 | Escalations and trough FVIII levels during the study period

At the end of the 2-year individualised prophylaxis, most patients (53%, $N = 31$) were in the group with trough level 1–3 IU/dl. Of the remaining

TABLE 2 Patients' baseline characteristics

	Value
Age, year	
Median (Quartiles)	5.3 (3.8, 6.9)
Mean (Range)	5.56 (.8–14.6)
Bodyweight, kg	
Median (Quartiles)	21.5 (16, 25)
Mean (Range)	22.52 (12-50)
Body Mass Index, kg/m^2	
Median(Quartiles)	16.12 (14.72, 17.54)
Mean(Range)	16.83 (13.43-27.43)
Blood group, N	
O:non-O	23:35
Dose,IU/kg	
Median(Quartiles)	21.7 (16.1, 27.9)
Mean(Range)	23.12 (5.3-53.3)
Dosing interval, day	
Median(Quartiles)	2.34 (2.0, 3.5)
Mean(Range)	2.75 (1.0-7.0)
Trough level, *N* (%)	
<1 IU/dl	34 (58.6%)
1-3 IU/dl	17 (29.3%)
3-5 IU/dl	7 (12.1%)
>5 IU/dl	0 (0%)
Target joint, *N*	
elbow	2
Knee	1
ankle	4

Abbreviation: N, number.

patients, 7(17%) remained at a trough level < 1 IU/dl, 9 (16%) were in trough level 3–5 IU/dl group and 8 (14%) patients in > 5 IU/dl group. Figure 3

During the study, there were a total of 47 escalations except for the last four escalations at 30th month (endpoint/study exit). Most of these escalations (28/47, 59.6%) were triggered by joint bleeds alone. Eight (17.0%) escalations were based on US evaluation alone, one by HJHS evaluation alone while one was determined by a combination of US evaluation, HJHS and joint bleeds. The number of escalations were 15 at the first follow-up (baseline), 17 at the 2nd follow-up (12th month), 10 at the 3rd follow-up (18th month), 5 at the 4th follow-up (24th month). Besides these 47 escalations, other 4 escalations were indicated by joint bleeds and US scores at endpoint (30th month), which did not have corresponding period to observe its influence due to the study exit Table 3.

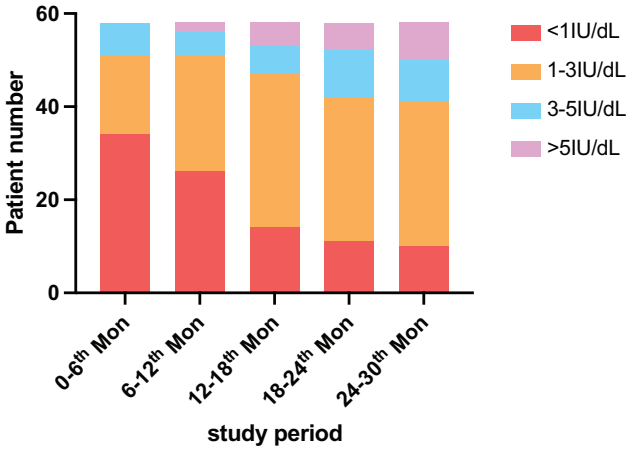

FIGURE 3 Patient number of different trough level groups among periods of study

3.3 | Clinical outcomes

3.3.1 | Bleeding rates

Table 4 showed the bleeding rates observed in these 58 patients. Compared with the ABR and AJBR at baseline, significant improvements have been demonstrated from the first 6-month of individualised prophylaxis [ABR:2(0,4) vs. 4(0,8), $p < .05$; AJBR, 0(0,2) vs. 2(0,4), $p < .05$] to study exit [ABR:0(0,2) vs. 4(0,8), $p < .0001$; AJBR, 0(0,.25) vs. 2(0,4), $p < .0001$]. The ZBP increased from 27.6% (16/58) at study entry to 60.9% (40/58) at study exit. ZJBP showed similar increased trend with reduction of 34.8% from baseline to endpoint. Similar improvement in ZSBP (84.5% vs. 43.1%) was also observed. Although the improvement of ZSBP ($p = .58$) and ZJBP ($p = .06$) did not reach statistical difference in the first 6-month of individualised prophylaxis period, the patient numbers with zero bleeds did increase significantly thereafter. Additionally, the seven target joints decreased to four by 18th month and to only one at study exit.

In our study, the patients were divided into a few trough-level groups (<1 IU/dl, 1–3 IU/dl, 3–5 IU/dl and >5 IU/dl) according to the WFH recommended trough level of 3 IU/dl and guideline of BSH which pointed out that baseline FVIII of 3–5 and >5 IU/dl had a different bleeding pattern and joint scores.[1,8] Figure 4 shows the zero bleeding proportions of each trough-level group (<1, 1-3, 3-5 and >5 IU/dl) at different study period. Since the study period (2.5 years) was divided into five 6-months, the zero bleeding proportions of each specific six-month was calculated according to the bleeding records of the patients who stayed in corresponding trough level group during that 6-month. Compared with 34 patients with low trough level (<1 IU/dl) at baseline, 10 patients in this trough level group (<1 IU/dl) at study exit demonstrated observable escalations in ZBP (60% vs. 21%), ZJBP (90% vs. 38%), ZSBR (80% vs. 41%) and ZSJBR (90% vs. 50%). Parallel results could also be found in the other three trough level groups. In addition,

TABLE 3 Escalations and their attributions

	6th month (baseline)	12th month	18th month	24th month	30th month (endpoint)
JB	12	8	5	3	3
JB+HJHS	0	3	0	0	0
JB+US	2	2	1	1	0
JB+US+HJHS	0	1	0	0	0
HJHS+US	0	0	0	0	0
HJHS	1	0	0	0	0
US	0	3	4	1	1
Total (proportion)	15 (31.9%)	17 (36.2%)	10 (21.3%)	5 (10.6%)	4

Abbreviations: HJHS, haemophilia joint health scores; JB, joint bleeds; US, ultrasound.
The data was depicted as number of escalations. The proportion of total escalations at each time point was also calculated without the 30th month because the lack of its corresponding follow-up period.

TABLE 4 bleeding rates of all patients in different period

	Observational period	Individualized prophylaxis period			
	0-6th month	6-12th month	12-18th month	18-24th month	24-30th month
ABR					
Median (lower quartile, upper quartile)	4(0,8)	2(0,4)	2(0,4)	0(0,4)	0(0,2)
Range	0–40	0–14	0–16	0–8	0–6
p value (vs. previous 6-month)		.01	.47	.08	.02
p value (vs. baseline)		.01	<.01	<.0001	<.0001
AJBR					
Median (lower quartile, upper quartile)	2(0,4)	0(0,2)	0(0,2)	0(0,2)	0(0,.25)
Range	0–26	0–12	0–12	0–8	0–6
p value (vs. previous 6-month)		.01	.84	.78	.04
p value (vs. baseline)		.01	<.01	<.001	<.0001
ZBP	27.6% (16/58)	48.3% (28/58)	50.0% (29/58)	60.3% (35/58)	69.0 (40/58)
p value (vs. previous 6-month)		.03	>.99	.35	.43
p value (vs. baseline)		.03	.02	<.001	<.0001
ZJBP	46.5% (27/58)	63.8% (37/58)	72.4% (42/58)	70.6% (41/58)	81.3% (47/58)
p value (vs. previous 6-month)		.09	.43	>.99	.28
p value (vs. baseline)		.09	<.01	.01	<.001
ZSBP	43.1% (25/58)	67.2% (29/58)	70.0% (40/58)	81.0% (47/58)	84.5% (49/58)
p value (vs. previous 6-month)		.58	.06	.19	.81
P value (vs. baseline)		.58	<.01	<.0001	<.0001

Abbreviations: ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; ZBP, zero bleeding proportion; ZJBR, zero joint bleeding proportion; ZSBP, zero spontaneous bleeding proportion.
ABR and AJBR were depicted as median (lower quartile, upper quartile) with range. *p* values were generated by paired Wilcoxon tests. ZBP, ZJBP and ZSBP were showed as patients number and proportion and *p* values were generated by Fisher's tests. All the comparisons were conducted both between first 6-months (baseline period) and other 6-months of individualized prophylaxis as well as between each 6-month and its previous six-month.

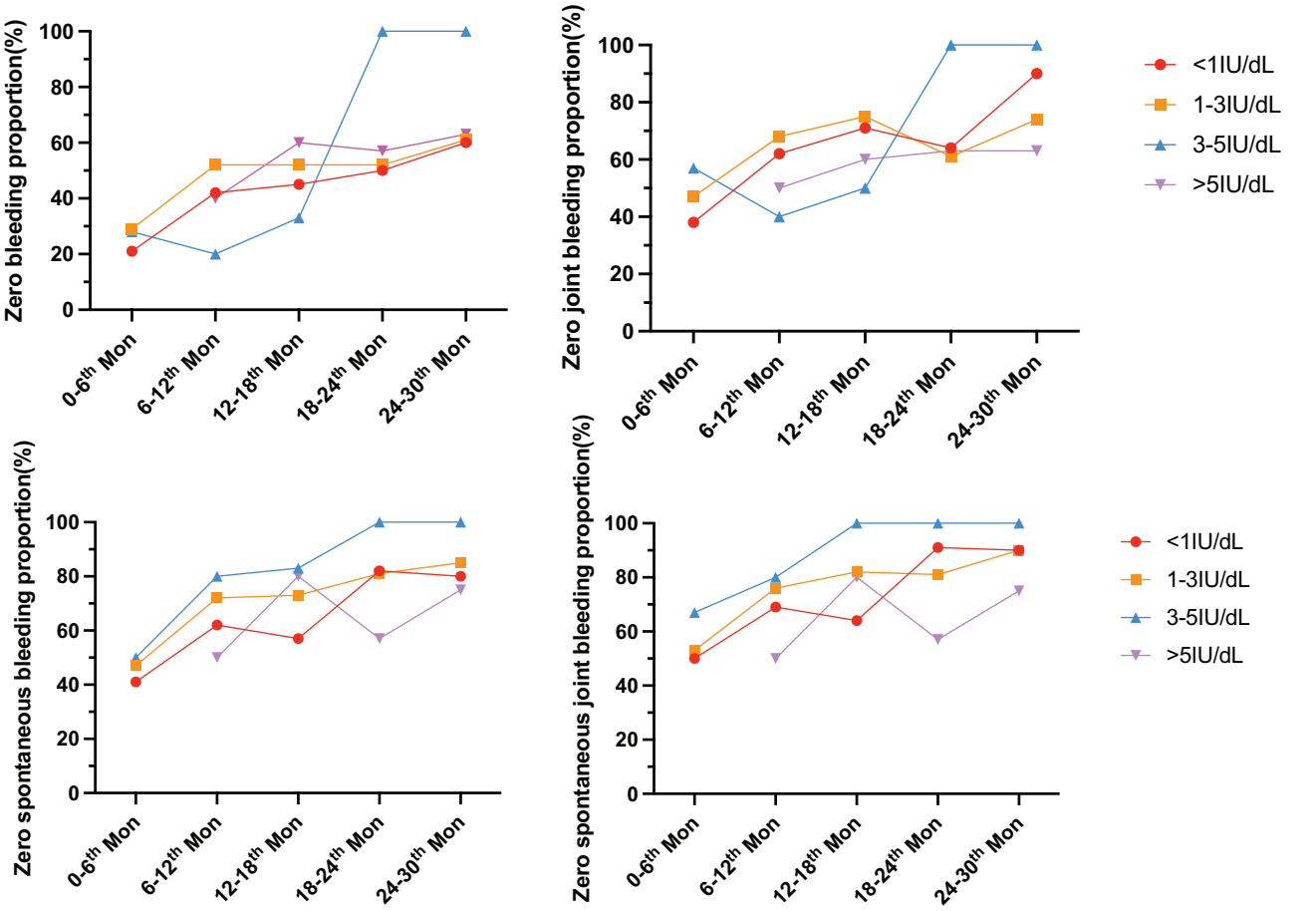

FIGURE 4 Zero bleeding rates in different trough level groups during the study

the patients in 3–5 IU/dl group showed a ZBP of 100% during the last 12 months (18th–30th month) of individualised prophylaxis period.

3.4 | US evaluation and HJHS results

Compared with scores at baseline, decreased US scores [Median: 2(1,5) vs. 2(1,5), $p < .05$; Mean: 3.4 vs. 4.0] and HJHS scores [Median. 0(0,2.25) vs. .5(0,4.5), $p < .05$; Mean: 1.6 vs. 2.5] were demonstrated at study exit. No statistical difference was found at 12th month in US scores [2(1,5) vs. 2(1,5), $p = .15$] and HJHS scores [0(0,3) vs. .5(0,4.5), $p = .11$].

3.5 | FVIII consumption and quality of life

Higher median weight-adjust FVIII consumption was observed at study exit [3500(2496, 5625) vs. 3129(2086, 4345) IU/kg/year, $p < .05$]. However, the infusion times per year was unchanged [156(104,182) vs. 158(106,188), $p = .54$]. No significant difference was observed in CHO-KLAT scoring scales both in parents' sheet (Main sheet, $p = .42$; SEC sheet, $p = .60$) and children's sheet (Main sheet, $p = .43$; SEC sheet, $p = .25$) Table 5.

4 | DISCUSSION

Although the importance of individualised prophylaxis has been emphasised by recent guidelines and recommendations, there has not been any detailed protocol to follow yet.[1,8] Some studies tried to set a fixed target trough level for patients with different bleeding phenotype or joint status and obtained improved clinical outcomes compared with bodyweight-based dosing regimen.[14–16] In a report of individualised prophylactic treatment with the help of population PK tool (MyPK-Fit), the authors demonstrated reduced ABR(-2.2 ± 1.3, $p < .05$) and AJBR(-1.9 ± 1.2, $p < .05$) while no significant difference was found in annual FVIII consumption.[14] Another study of PK-tailored prophylaxis demonstrated an overall FVIII consumption reduction of 7.2% and the possibility of extending the dosing interval while maintaining well controlled bleeds.[16] However, a fixed target trough level also meant the lack of individualisation in determining personalised FVIII level. Other studies made adjustment according to the observations of unaccepted bleeds and joint deterioration.[17,18] Unluckily, since every centre has its own standard to determine when and how to adjust the dosing regimen, there were no clear or detailed standards to follow, which limited its widespread adoption.[19] Instead, we adopted a detailed joint evaluation system with quantitative scoring system. Along with the most

TABLE 5 Quality of life and FVIII consumption

	Baseline	Study exit	*p value*
CHOK-LAT scoring sheet			
Parents' main sheet	68.57 (60.53,78.83)	71.79 (61.29,81.79)	.42
Parents' SEC sheet	72.22 (61.11,84.38)	77.78 (64.02,88.28)	.60
Children's main sheet	82.14 (72.86,87.14)	81.79 (68.53,90.18)	.43
Children's SEC sheet	80.56 (63.89,83.33)	83.34 (75.84,92.19)	.25
FVIII consumption and infusions per year			
FVIII consumption (IU/kg/year)	3129 (2086,4345)	3500 (2496,5625)	<.05
Infusions (per year)	156 (104,182)	156 (106,188)	.54

Abbreviations: CHOK-LAT, Canadian Haemophilia Outcomes-Kids Life Assessment Tool; SEC sheet, Socio-Economic Context sheet. The data were depicted as median and interquartile. *p* values were calculated by paired Wilcoxon tests.

widely used PK dosing tool (WAPPS-Hemo), our protocol provided a new practical way to optimise prophylaxis by individualising target trough level gradually.

The first advantage is the integration of the PK tool, which helped us have a better knowledge and design of patients' therapy and a PK-based escalation of trough level could achieve simultaneously. The patients with trough level < 1 IU/dl showed a reduction of 41% (24/58) at study exit, suggesting that a large proportion of our patients had under-treatment at baseline. Urgent request of a higher trough level was also revealed by the low zero bleeding proportions of different trough level groups at study entry. This was in accordance with other well conducted studies before.[20,21] During the individualised prophylaxis period, the most escalations (59.6%) were due to the joint bleeds alone. But if joint bleed is the only criteria for escalation, dose adjustment would not have been performed in the remaining 40.6% in lack of systematical evaluation. In addition, 13.8% of the escalations were conducted by US detection alone, which demonstrated the heterogeneity in patients' joint response to haemorrhage. Although US and HJHS have been applied in routine therapy of children with haemophilia A, our study innovatively developed a quantitative joint evaluation system which included joint bleeds as well as US and HJHS.[22,23] With our detailed and clear protocol, utilisation and promotion would be easy.

The improved clinical outcomes could be demonstrated by the rapidly decreased bleeding rates and reduced joint scores of our patients. The reduction of ABR/AJBR has reached statistical difference since the first six-month of individualised prophylaxis. The increments in ZBP (27.6%–69.0%), ZSBR (43.1%–84.5%) and ZJBP (46.5%–81.3%) among all patients indicated the effectiveness of this protocol in bleeding control as well. The results of US and HJHS did not reach a significant difference until the study exit. This indicated that a long observational period of at least 2 years should be taken to track the change of joint state because joint repair is a long process. Similar non-statistical reduction of .5(median) in US cores and 3.0(median) in HJHS was also found in CHIPS study which took a step-up dosing regimen design with one year study period.[17] The minimal detectable change of our HJHS is 1.0 score and the only fixed rehabilitation physician also eliminated the potential inter-judge variability. Although the change of median HJHS was small (median: .5), the consist trend of improving and significant reduction at end of study did reveal the benefits. In addition, considering the significant reduction of joint scores at study exit and the elimination of most target joints (6/7) as well as the observed reduction of AJBR, our new prophylactic strategy suggests a promising effective joint protection if this protocol is well adhered to.

Another advantage of our study is that we provided a practical assay to explore patients' individualised target FVIII levels, which has hardly been investigated before. With the help of individualised PK profiles, the dosing regimen of patients were continually adjusted until an ideal target trough level is reached. During the last six-month period, the ZBP of patients in trough level <1 IU/dl group has increased to 60%, which is even higher than the 1–3 IU/dl group (40%) and similar to the 8–12 IU/dl group (67%) of PROPEL study. This should attribute to the effective differentiation of patients with various bleeding phenotypes and trough level request by this protocol. Besides ZBP, the ZJBP and ZSBR of all groups finally reach a very high level of more than 60% and most of them were over 80%. The increased ZSBP also indicated the substantial improvement in their routine prophylaxis. What's more, the patients in 3–5 IU/dl did not suffer from any kind of bleeds in the last 6-month of individualised prophylaxis period, indicating the well achieved target trough level range for these patients. To our notice, patients in trough level >5 IU/dl group showed the lowest values in all kinds of zero bleeding proportions, which seemed to be unreasonable at first glance. However, considering all these patients come from lower trough level groups before, they actually represented those with severe bleeding phenotype and higher target trough level. For these patients, ZBP might be achieved only with a very high trough level, such as the previously reported 12–15 IU/dl.[24,25] Thus, optimised clinical outcomes could also be obtained with individualised target trough levels instead of simply going for a fixed high trough level (like full-dose prophylaxis). This was also in accordance with the classical investigation conducted by Uilj et al. which demonstrated that although the AJBR reduced very fast with trough level escalated within 1–5 IU/dl, the aim of zero bleeds was only reached with a high trough level of over 12 IU/dl.[25]

Compared with the patients in high trough level group (8-12 IU/dl) in the well-designed PROPEL study, our patients showed much lower

trough levels (with only eight individuals >5 IU/dl) but very similar ZBP(69% vs. 62.0%) and ZJBP(81.3% vs. 76%).[26] Furthermore, the dosage used in our patients was only half that of PROPEL's [3500(2496,5625) vs. 7490(4771.6,9903) IU/kg/year] with lower number of infusions per year [156(106,188) vs. 179.4(163.6, 188.5) infusions per year]. Since no extended half-life FVIII concentrates has been approved in China, the short half-life of standard half-life products request frequent infusions and high dose to escalate trough FVIII level, which might prevent improvements on patients' quality of life.[27] Besides, many children are restricted to physical activity by their parents to reduce the risk of bleeding which would partially mask the benefits of adjusted new dosing regimen. Thus, the lack of statistical difference of the CHOK-LAT scores between baseline and study exit could be explained. Considering our study gave very detailed and clear protocol, this clinical application would not be hard. In addition, the PK profiles and calculations are easy to conduct with the widespread of online PK tools like WAPPS-Hemo.

Although we provided a very detailed and clear protocol, wide clinical applicability should be careful. In our study, the scores for escalation include joint bleeds which did not distinguish if it is a spontaneous or traumatic one. For patients on good prophylaxis, traumatic bleeds still could happen along with accidental situation or physical activity. In developing countries like China, physical activity of children with haemophilia were always suppressed and that's why the escalation of trough level could bring significant reduction in bleeding rates and the score system works. While in some developed countries where children with haemophilia were reported with very similar sports anticipation with their peers, almost all bleeds were caused by injury. Thus, their caregivers might consider different things like lifting their peak level. In addition, the obvious exclusions of patients (from 117 to 58) were caused by our high requirements for compliance (patients with any deviation of the protocol would be excluded). Therefore, this manuscript could guarantee the accurate efficacy report of this study. However, its representative of the real-life practice reduced, and attention should be raised in clinical application. Also, the patient number of some trough level groups was small due to the division, which calls for carful interpretation.

5 | CONCLUSION

The results of our study showed its potential ability to individualise target trough level and achieve optimal clinical outcomes in paediatric patients with severe haemophilia A. This protocol could obtain wide attention both in source-limited and developed regions due to its ability of facilitating an optimal utilisation of FVIII concentrates with maximum effectiveness and minimum waste.

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CONFLICT OF INTEREST

The authors confirmed that there are no interests.

AUTHOR CONTRIBUTIONS

Kun Huang conducted the PK tests, collected the data, analysed the data, and wrote the manuscript. Di Ai collected the clinical data and did some analysis. Yingzi Zhen and Xinyi Wu helped with blood sampling. Gang Li devoted to laboratory tests. Ningning Zhang did the ultrasound tests and calculated scores. Yang Wang conducted the clinical joint evaluation (HJHS). Guoqing Liu provided support of clinical follow-ups. Zhenping Chen and Runhui Wu proposed this study, reviewed the manuscript and approved the submission. Kun Huang and Di Ai share the co-first authorship of this work. The manuscript has been read and approved for submission by all authors.

DATA AVAILABILITY STATEMENT

The data could be available upon reasonable request to corresponding author.

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