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Significant PK variability of plasma-derived FIX concentrates in chinese children with Haemophilia B: A fixed single-dose study of factor IX-CTBB

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ABSTRACT

Background: The pharmacokinetics (PK) characters of plasma-derived Factor IX (pdFIX) concentrate in Chinese children with Haemophilia B(HB) have not yet been reported.
Aim: To assess the PK parameters of pdFIX in children with severe HB and identify factors that influence FIX PK.
Methods: This non-randomized, open-label PK study enrolled children with severe HB (FIX ≤ 2 %). Patients received 50 IU ± 5 IU/kg pdFIX (Human coagulation Factor IX-CTBB) after at least 96 h wash-out period. Blood samples for PK assessments were collected before infusion (pre-dose) and at 15 min, 30 min, 1 h, 3 h, 6 h, 9 h, 24 h, 48 h, 72 h and 96 h post-infusion. FIX activity was measured by a one-stage assay.
Results: Twenty patients were enrolled with a median age of 8.3 (range 1.8–15.4) years. The peak plasma levels of FIX: C in all patients were observed within 15 min. Their median terminal half-life ($t_{1/2}$) was 32.6 (range 23.3–52.0) hours. The median values of in vivo recovery (IVR) at 15 min, clearance (CL), volume of distribution at state (Vss) and area under the curve (AUC) were 1.0 (0.9, 1.2) IU/dL per IU/kg, 5.2 (IQR 4.8, 6.4) mL/h/kg, 207.9 (IQR 183.5, 301.4) mL/kg, 9.77 (IQR 7.76, 11.23) U*h/mL respectively. The $t_{1/2}$, Vss and mean residence time after intravenous injection (MRT) decreased with increasing age and body weight. Changes in CL with body weight were similar to $t_{1/2}$, but no significant correlation exists with age.
Conclusions: There is a significant inter-individual variability in PK profiles among Chinese children with severe HB, which is related to age and body weight changes, indicating the necessity of individualized prophylaxis driven by PK.

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Introduction

Haemophilia B (HB), a rare X-linked genetic deficiency of coagulation factor IX (FIX) resulting from mutations in the F9 gene, affects approximately 1 in 100,000 live male births[1]. The main clinical manifestations of HB include various types of bleeding and difficulty in stopping bleeding. Chronic and repeated bleeding into the joints can lead to irreversible damage to joint structures, potentially resulting in severe arthropathy if not appropriately managed, particularly in individuals with severe and some moderate forms of HB[2]. Prophylaxis has been shown to reduce bleeding events, with the World Federation of Haemophilia (WFH) recommending it as the standard care for severe HB and non-severe HB with a severe phenotype.

Clinically, patients with haemophilia treated with similar regimens may have very different outcomes. Dose calculations for most weight-based prophylactic regimens have been performed with the assumption that all patients exhibit similar pharmacokinetic (PK) characteristics. However, there is substantial inter-individual variability in various PK parameters, such as half-life time ($t_{1/2}$), clearance (CL), and in vivo recovery (IVR)[3]. Current guidelines broadly recommend using PK-guided prophylaxis in hemophilia to optimize factor concentrate consumption and improve clinical outcomes[1]. This approach has shown good treatment results in haemophilia A and is increasingly used, but has limited details regarding HB. The metabolism of FIX does not follow the same pattern as FVIII. A potentially important consideration in directing treatment based solely on the plasma levels of administered FIX is the difference in the distribution in the intra- and extravascular components for FIX [compared with factor VIII (FVIII)] and between different FIX therapeutic agents in people with HB[4]. To ensure optimal prophylaxis and cost-effective factor use, clinical guidelines and expert groups recommend that treatment for HB should be individualized. Such personalisation involves adjusting the dosing based on the PK properties of the FIX concentrates while considering each patient's clinical situation and disease severity[5].

Human coagulation Factor IX-CTBB (FIX-CTBB) , the first domestically produced highly purified plasma-derived FIX concentrate in China, is prepared using three consecutive chromatography steps and utilized for treating and preventing bleeding in individuals with HB [6]. However, the PK characters of this product in HB patients aged < 16 years have not previously been reported in China. It presents challenges for clinicians in determining optimal individual dosing regimens for patients with HB. Therefore, this research aims to elucidate the PK profile of Factor IX-CTBB in Chinese pediatric patients with HB, providing clinicians with essential information for effective clinical bleed prevention and control.

Materials and methods

Ethics approval

The study was approved by the ethics committee of Beijing Children's Hospital and conducted according to the Declaration of Helsinki. Written informed consent was obtained from each enrolled patient and their legally authorized guardian(s). The study was registered in ClinicalTrial.gov as ChiCTR2200059494.

Patients

Patients with severe HB were enrolled at Beijing Children's Hospital between May 2023 and February 2024. The inclusion criteria were age 1–16 years; severe HB (FIX activity ≤ 2 IU/dL); receipt of prophylactic treatment with a FIX-CTBB. The exclusion criteria were the presence of a current FIX inhibitor (anti-FIX antibody titer > 0.6 Bethesda units per mL), active bleeding or a concurrent coagulation disorder.

Clinical data collection

Baseline FIX: C levels, age, and blood group were obtained from the medical records. Weight and height were measured at the time of the first blood collection for PK.

Blood samples

After a wash-out period of at least 96 h, each patient received an infusion of FIX-CTBB at doses of 50 ± 5 IU/kg. Peripheral venous blood samples were drawn using two 2 mL vacutainer tubes with 3.2% trisodium citrate. A previously reported blood sampling strategy was used (pre-dose, 15 min, 30 min, 1 h, 3 h, 6 h, 9 h, 24 h, 48 h, 72 h and 96 h after concentrate infusion) as described previously[7]. After that, all blood samples were immediately centrifuged at 2500 ***g*** for 15 min at room temperature (20–25 ˚C) for poor platelet plasma. Plasma was divided into two Eppendorf tubes (400 μl per tube) and stored in a -80 ˚C freezer for further analysis.

Laboratory assay

The one-stage-based activated partial thromboplastin time assay measured FIX activity (FIX: C) in a multi-dilution mode, using HemosIL® FIX deficient plasma (Instrumentation Laboratory, Bedford, MA, USA). The APTT reagent is HemosIL® SynthAsil (Instrumentation Laboratory, Bedford, MA, USA). The Nijmegen modification of the Bethesda assay was used to determine the levels of FIX inhibitors. An ACL TOP-700 analyzer was used to perform all measurements (Instrumentation Laboratory, Bedford, MA, USA).

All samples from the same individual were tested in the same batch to ensure consistency. Pre-infusion points were tested simultaneously for FIX inhibitors.

PK analysis

The PK analysis of FIX-ICBB was based on FIX: C levels and performed using WAPPS-Hemo (https://www.wapps-hemo.org) [8]. This study entered the following information into WAPPS: patient number, age, height, body weight, baseline FIX: C level, dose, precise blood sampling time, corresponding FIX: C levels of all samples, and FIX measurement assay. The PK parameters, including half-life time ($t_{1/2}$), clearance (CL), in vivo recovery (IVR), volume at steady state (Vss), mean residential time (MRT) and area under the curve (AUC), were all analysed. IVR was also calculated as follows: IVR (IU/dL per IU/kg) = (Cmax − $FIX_{reinfusion}$[IU/dL])/($FIX_{administered}$ [IU/dL]/body weight [kg]).

Statistical analysis

The statistical analysis and the figure generation were performed using GraphPad Prism for Mac (Version 9.0.1). Normally distributed data were reported as mean ± standard deviation, while non-normally distributed data were reported as median (upper quartile, lower quartile). Since most of the data was non-normally distributed, Wilcoxon tests were used to evaluate the difference. Spearman correlation coefficient was used to analyze the potential relations. A p-value < 0.05 indicated a statistically significant difference.

Results

Patient characteristics

Twenty patients were enrolled in the study, all with FIX: C below 2 %. The median age is 8.3 years (range 1.8–15.4), with a median body weight of 33.5 kg (range 12.0–70.0) and a body mass index of 17.9 kg/m^2 (range 14.6–24.7). All patients tested negative for FIX inhibitors (< 0.6BU/mL). Seven patients were younger than six years of age, and 13 were between 6 and 15 years of age. Detailed demographic details of the patients are shown in Table 1.

PK parameters of FIX concentrates

The FIX: C levels at different time points following a single dose of FIX-CTBB were shown in Fig. 1. Except for one patient (FIX: C= 5.5 % at pre-infusion) , the pre-infusion FIX: C of all other patients is < 5 %, indicating an adequate wash-out period of PK analysis. All patients reached peak FIX: C plasma levels within 15 min post-infusion. The respective median values of $IVR_{15\ min}$, $IVR_{30\ min}$ and $IVR_{60\ min}$ were 1.0 IU/kg per IU/dL, 0.9 IU/kg per IU/dL and 0.8 IU/kg per IU/dL (Table 1). The $IVR_{15\ min}$ was significantly higher than $IVR_{30\ min}$ and $IVR_{60\ min}$ ($P = 0.002$; $P < 0.001$).

The median $t_{1/2}$ is 32.6 (IQR 30.6, 43.0) hours, ranging from the longest $t_{1/2}$ of 52 h to the shortest $t_{1/2}$ of 23.3 h. Such data indicate that the longest $t_{1/2}$ is nearly twice as long as the shortest $t_{1/2}$. The median CL is 5.2 (IQR 4.8, 6.4) mL/h/kg, and the AUC is 9.77 IU*h/mL (IQR 7.76, 11.23). The PK parameters are shown in detail in Table 2.

The correlations between PK parameters were then assessed, with results indicating no significant correlation between $t_{1/2}$ and CL (r = 0.081, $P = 0.736$) or AUC (r = −0.251, $P = 0.286$). However, the $t_{1/2}$ showed a significant positive correlation with Vss (r = 0.870, $P < 0.001$) and MRT (r = 0.985, $P < 0.001$). (Fig. 2).

Factors influencing PK parameters

Age

The cohort was divided by age into two groups: those younger than six years old and those older than six years old. A comparative analysis of PK parameters was conducted between the two groups. Patients below six years of age exhibited a longer $t_{1/2}$ compared to patients above six years of age [45.5 (43.0, 51.3) vs. 31.6 (30.2, 33.4), $P = 0.001$]. Vss and MRT were higher in patients younger than six years old than in patients older than six years of age [Vss: 358.3 (301.4, 412.3) vs. 187.7 (166.1, 220.3), $P = 0.001$; MRT: 59.7

Table 1
Patients' baseline characteristics and demographics.

	Younger children (≤6 years)	older children (6-15 years)	Total
Number of patients	7	13	20
Age, years	3.5 (1.7, 5.8)	11.0 (8.3, 13.5)	8.3 (4.7, 12.0)
Heigh, cm	98.0 (90.0118.0)	150.0 (140.5, 163.0)	140.5 (107.5, 158.0)
Weight, kg	14.0 (12.0, 14.5)	48.0 (32.0, 60.5)	33.5 (17.6, 48.7)
Body mass index (BMI), kg/m^2	14.8 (14.7,18.6)	18.8 (15.9, 22.0)	17.9 (15.3, 21.3)
Fat-free body (FFM), kg	13.2 (11.3,18.3)	39.0 (29.5, 47.5)	29.5 (16.4, 42.0)

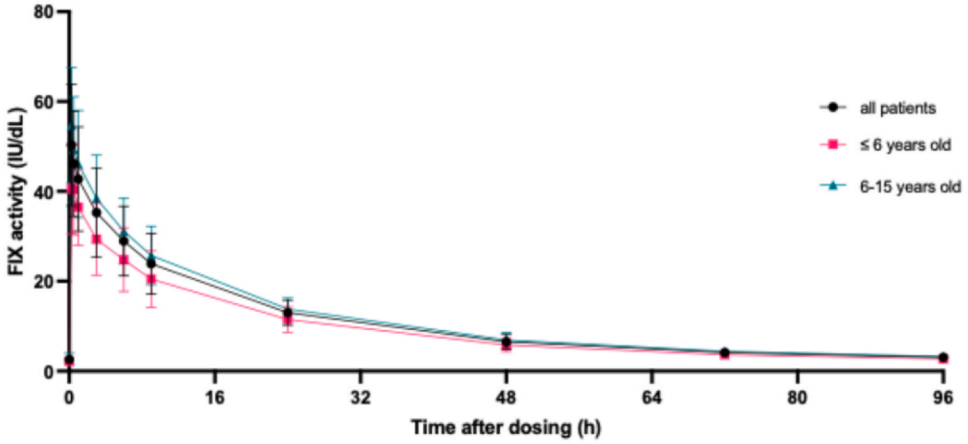

Fig. 1. Plasma FIX concentration (mean ± standard deviation) vs time curve of FIX-CTBB after a single infusion, presented within two age groups.

Table 2
Patients' PK parameters.

	Median (IQR)	Range
$t_{1/2}$	32.6 (30.6,43.0)	23.3 – 52.0
CL (mL/h/kg)	5.2 (4.8, 6.4)	3.5 – 7.1
$IVR_{15\ min}$ (IU/dL per IU/kg)	1.0 (0.9, 1.2)	0.7 – 1.4
$IVR_{30\ min}$ (IU/dL per IU/kg)	0.9 (0.8, 1.0)	0.6 – 1.3
$IVR_{60\ min}$ (IU/dL per IU/kg)	0.8 (0.7, 0.9)	0.6 – 1.3
AUC (IU*h/mL)	9.77 (7.76, 11.23)	5.83 – 14.34
MRT(h)	39.1 (36.2, 54.6)	25.5 – 73.4
Vss (mL/kg)	207.9 (183.5, 301.4)	127.7 – 421.3

$t_{1/2}$, halflife time; IVR, in vivo recovery; CL, clearance; Vss, volume at steady state; MRT, mean residential time; and AUC, area under curve.

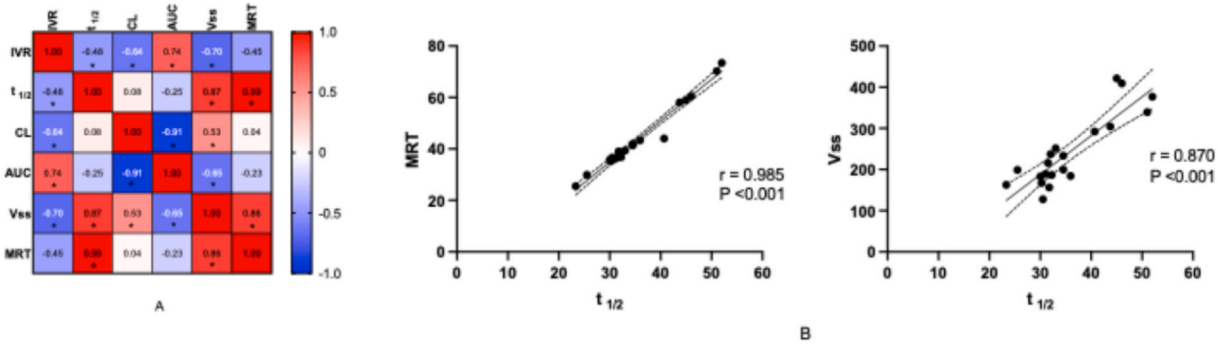

Fig. 2. Correlation of pharmacokinetic (PK) parameters. A. Correlation coefficient heatmap considering PK parameters; B. Correlation of $t_{1/2}$ with MRT and Vss. $t_{1/2}$, half-life time; IVR, in vivo recovery; CL, clearance; Vss, volume at steady state; MRT, mean residential time; and AUC, area under curve; *, $P < 0.05$.

(54.6, 71.0) vs. 36.7 (35.6, 39.9), $P = 0.001$]. There was no statistically significant difference in IVR, CL, and MRT between the two age groups, as shown in Fig. 3A. Further analysis in all patients revealed that $t_{1/2}$, Vss and MRT decreased with increasing age ($r = -0.779$, $P < 0.001$; $r = -0.838$, $P < 0.001$; $r = -0.766$, $P < 0.001$) (Fig. 3B). The $t_{1/2}$ decreased consistently by 1.4 h/year (regression coefficient: −1.403 [CI: −1.963– −0.843]). However, a trend of $t_{1/2}$ increasing with age was observed in three patients over 12 years old.

Weight

Fig. 4 shows the association between body weight, BMI, FFM and PK parameters. The $t_{1/2}$, CL, Vss, and MRT decrease with increasing body weight ($r = -0.780$, $P < 0.001$; $r = -0.511$, $P = 0.021$; $r = -0.880$, $P < 0.001$; $r = -0.744$, $P < 0.001$). In contrast, IVR and AUC increase with increasing body weight ($r = 0.609$, $P = 0.006$; $r = 0.550$, $P = 0.012$). The correlation of weight and FFM with PK parameters is similar to that of FFM. Body weight and FFM correlated more strongly with PK parameters.

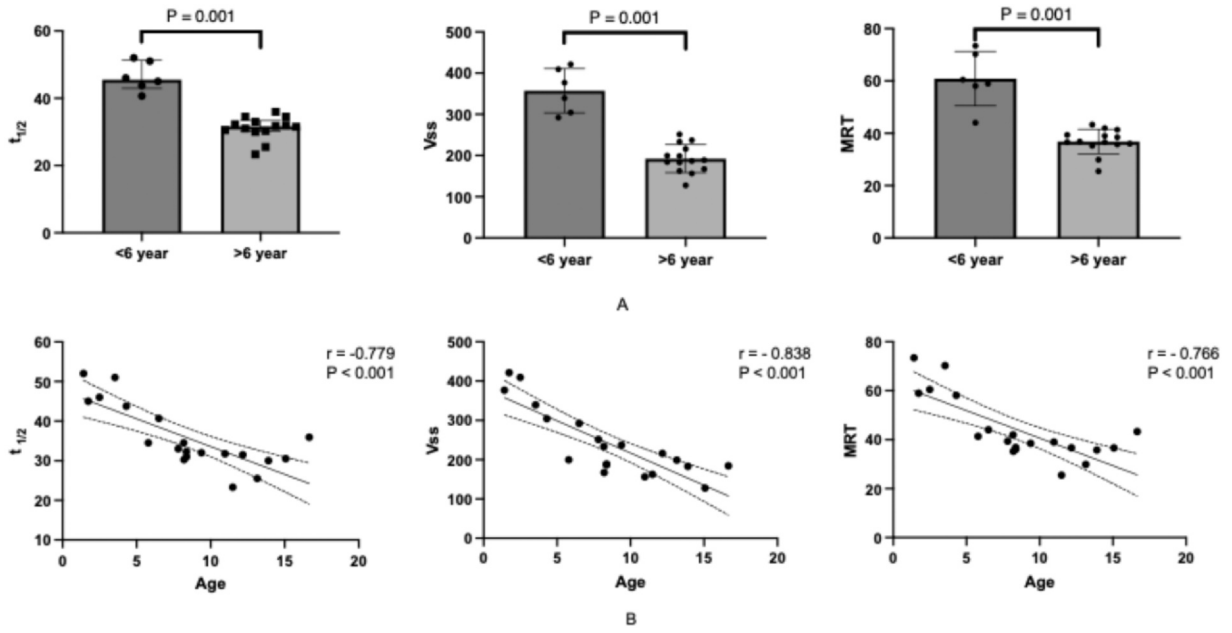

Fig. 3. Effect of age on PK parameters. A Compare PK parameter between the groups of children over six years old and those under six years old ; B Correlations of Age with PK parameters. $t_{1/2}$, half-life time; Vss, volume at steady state; and MRT, mean residential time;.

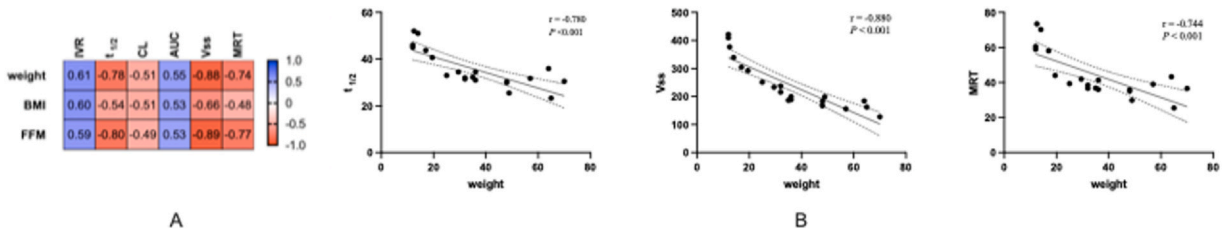

Fig. 4. Correlations of weight, BMI, FFM with PK parameters ($t_{1/2}$, IVR, CL, Vss, MRT and AUC). A Correlation coefficient heatmap of weight, BMI, FFM with PK parameters; B Correlations of weight with MRT and Vss. BMI, Body Mass Index; FFM, fat-free body; $t_{1/2}$, half-life time; IVR, in vivo recovery; CL, clearance; Vss, volume at steady state; MRT, mean residential time; and AUC, area under curve;.

Blood group

The relationship between blood grouping and PK parameters was also examined, with no statistical difference found in all PK parameters between blood groups O and non-O.

Discussion

Individual PK testing has emerged as an essential tool for tailoring prophylactic treatments for patients with hemophilia, given the considerable inter-individual variability. This study presents the PK profile of HB in Chinese children for the first time, emphasizing the importance of personalized treatment strategies.

Outcomes from this study are comparable with those previously reported regarding the standard half-life (SHL) FIX PK parameter, which has a longer $t_{1/2}$ and lower IVR than FVIII. In the current study, the median $t_{1/2}$ of FIX-CTBB is 32.6 h. Olav Versloot showed that the $t_{1/2}$ of SHL-FIX was 34.1 (29.3–39.0) in 106 children with HB from the WAPPS database[9]. The IVR in the current study is 0.97 (0.71, 1.44) IU/kg, which is congruent with the previously reported average IVR range of 1.0 to 1.7 IU/dL per IU/kg for HB patients[9,10]. This study reported that the IVR reaches its zenith at 15 min post-infusion, corroborating the findings of J. A. Aznar's PK analysis of another pdFIX product (Grifols), where plasma FIX: C levels peaked within the first 30 min[11]. Notably, the PK profiles of HB are different from those of hemophilia A, primarily due to the unique extravascular distribution of FIX[12,13]. Approximately 40 % of the infused FIX is distributed in the lymphatic system or binds to subendothelial space type IV collagen[14]. The binding to endothelial cells and type IV collagen occurs primarily at the K5 residue of the FIX-Gla domain. rFIX with different K5 domain mutations has been used to explore and confirm the extravascular distribution of rFIX[15]. The reversible diffusion into the extravascular compartment, where the drug quantities in both intravascular and extravascular spaces are in a state of kinetic equilibrium, may correlate with the extended $t_{1/2}$ and lower IVR of FIX in contrast to FVIII[16].

This study also reveals a considerable range in the $t_{1/2}$ of pdFIX among the participants, with the longest recorded at 52 h and the shortest at 23.3 h, an approximately twofold difference between the extremes. This pronounced disparity highlights the notable inter-individual variability in the PK of HB patients, a critical consideration for the treatment regime. The findings from the current study align with prior research, which documented significant variation in the PK profile of pdFIX, with reported $t_{1/2}$ ranging between 15 to 50 h [17]. Comparable findings were also made concerning IVR, CL and other PK parameters, which could lead to substantial discrepancies in FIX dosing in traditional dosing regimens. Thus, PK of patients should be utilized to tailor individual prophylaxis in pediatric patients experiencing HB.

The pharmacokinetics of FIX are more complex than FVIII, with the current study reporting that $t_{1/2}$ had no significant correlation with CL but had a strong correlation with Vss. This correlation may relate to the characteristics of extravascular FIX distribution and the body structure across. The more pronounced distribution of pdFIX in the extravascular space compared to rFVIII. The total and extracellular water in the body decreases with age[18]. Similarly, the absolute values of the volume of distribution of FIX concentrates increase with weight and age until 18–20 years of age[19]. Therefore, the pharmacokinetic changes of FIX may be more pronounced during childhood. Unfortunately, the extravascular compartment is not readily accessible in humans, and all experimental PK data pertain only to the concentration of the drug available in plasma. The intricate pharmacokinetics of FIX, influenced by factors such as distribution characteristics and body composition. This also presents challenges for establishing population pharmacokinetic models. Our data show that body weight, FFM and BMI all correlate with pharmacokinetic parameters, with body weight and FFM showing stronger correlations. As body weight is more convenient to apply in the clinic than defatted body weight, it can be used as a covariate in future modelling of population pharmacokinetics. This provides valuable information for the development of population pharmacokinetic models to more accurately predict the dynamics of FIX in different patient populations. Such models hold significant value for optimizing FIX concentrate regimens and enhancing the precision of treatment strategies for individuals with HB.

The current study investigates factors affecting PK in HB patients, and the data validates that age significantly influences PK parameters. Specifically, we observe a significant inverse correlation between age and t1/2 of FIX during childhood, with younger patients exhibiting a longer $t_{1/2}$. Fewer studies have reported the relationship between age and $t_{1/2}$ in childhood, with inconsistent outcomes. Björkman's study of 56 subjects, including 11 children aged 4–10, reported no correlation between the $t_{1/2}$ and age for rFIX [9]. Olav Versloot showed that $t_{1/2}$ increased with age in FIX for subjects up to 30 years, but this study included HB using pdFIX or rFIX from the WAPPS database[20]. As rFIX is biochemically similar but not identical to pdFIX, the pharmacokinetic properties of the two molecular species may differ. The influencing factors of FIX pharmacokinetics vary substantially between different products and age groups. Notably, this study exclusively includes pediatric patients (ages 2–15 years) receiving the same pdFIX injections, enhancing the accuracy of the results. The Chinese PK profiles are based on eleven-time point curves, with a standard dose administration and an adequate wash-out period. Furthermore, all specimens from the same individual were tested using the same batch of reagents, minimising experimental error and ensuring the reliability of our findings. Predictably, the conclusion from this study needs to be further verified with a larger cohort of participants.

The current study has some limitations. Firstly, only the one-stage assay was used to test FIX levels, whereas the chromogenic assay would enable more reliable data to be considered. Another limitation is the small number of cases in different age groups during childhood.

Conclusion

Our study delineated the PK characteristics of Chinese children with HB and highlighted significant inter-individual variability in PK profiles. We confirmed that the PK characteristics of pdFIX are influenced by factors such as age and body weight. Consequently, individual patient PK profiles should be leveraged to tailor prophylactic treatment in pediatric HB and achieve better outcomes.

The current study will enable the adjustment of the participants' dosing regimens and could potentially support other additional studies and clinical questions. The present study and future investigations should facilitate the application of PK-tailored dosing of FIX concentrate in routine clinical practice.

Author contributions

Zhenping Chen and Runhui Wu proposed this study, reviewed the manuscript and approved the submission. Guoqing Liu and Di Ai conducted the PK tests, collected the data, analyzed the data, and wrote the manuscript. Yingzi Zhen and Xinyi Wu helped with blood sampling. Gang Li devoted to laboratory tests. Wanru Yao and Yunyun Wei did some analysis. Zekun Li and Yaohan Zhou collected some data. Guoqing Liu 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

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

Declaration of Competing Interest

The authors confirmed that there are no interests.

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