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Perioperative blood management and clinical outcomes in patients with hemophilia undergoing total joint arthroplasty: Our long-term results

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Hemophilia is a severe hereditary bleeding disorder characterized by a deficiency in coagulation factors. Patients often suffer from recurrent intra-articular hemorrhages, which eventually lead to hemophilic arthropathy (HA), a condition which severely compromises joint function and quality of life.[1] For patients with end-stage HA, total joint arthroplasty (TJA), including total knee arthroplasty (TKA) and total hip arthroplasty (THA), is widely regarded as the gold standard for alleviating chronic pain and restoring mobility.[2,3]

However, TJA is inherently associated with a high risk of significant perioperative hemorrhage, with total blood loss (TBL) in patients without hemophilia often exceeding 1,500 mL.[4] Given the

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ABSTRACT

Objectives: This study aims to evaluate the efficacy and safety of a comprehensive, multidisciplinary perioperative blood management (PBM) protocol in patients with Hemophilia A undergoing total joint arthroplasty (TJA).

Patients and methods: Between December 2014 and November 2024, a total of 29 male patients (mean age: 33.38±8.62 years; range, 20 to 55 years) with hemophilic arthropathy (HA), all diagnosed with Hemophilia A, who underwent total knee arthroplasty (TKA) or total hip arthroplasty (THA) were retrospectively analyzed. All patients received a standardized PBM protocol, including preoperative factor VIII sensitivity testing, individualized factor replacement, restrictive fluid management, ultrasound-guided regional anesthesia, and tranexamic acid administration. Primary outcomes included total blood loss (TBL) and hemoglobin (Hb) drop. Secondary outcomes included operation time, length of hospital stay (LOS), and perioperative complications.

Results: All 29 procedures were successfully completed under our PBM protocol. For the entire cohort, the median TBL was 630.52 (range, 470.95 to 939.64) mL, and the mean Hb decrease on postoperative Day 5 was –41.83±22.81 g/L. The median operative time was 122.0 (range, 91.0 to 182.5) min, and the median LOS was 23.0 (range, 19.0 to 31.0) days. Simultaneous double TJA showed higher TBL and transfusion rates than single TJA, but the outcomes remained within safe clinical limits. Furthermore, THA was associated with significantly shorter operation time (p = 0.008) and lower total FVIII consumption (p = 0.036) compared to TKA, despite similar TBL (p = 0.860). No major complications, such as inhibitor development, hemorrhage or venous thromboembolism were observed.

Conclusion: A standardized, multidisciplinary PBM protocol ensures surgical safety in patients with end-stage HA. Despite the underlying hemorrhagic diathesis, optimized factor replacement and comprehensive anesthetic strategies can achieve surgical outcomes comparable to the general population. These findings support the broader clinical application of comprehensive PBM for high-risk hemophilic surgical cases.

Keywords: Factor replacement, hemophilic arthropathy, perioperative blood management, total joint arthroplasty.

underlying coagulopathy, managing patients with hemophilia during TJA presents an even more formidable challenge for anesthesiologists and surgeons. While existing management protocols primarily focus on coagulation factor replacement therapy, there is a relative lack of emphasis on comprehensive perioperative blood management (PBM), including optimized anesthetic techniques and the systematic use of antifibrinolytic agents. Furthermore, certain recommendations in local expert consensuses remain subjects of ongoing clinical debate.[5,6]

In the present study, we aimed to evaluate clinical outcomes of patients with hemophilia A who underwent TKA or THA to provide a robust clinical reference for PBM in this high-risk population.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Department of Anesthesiology between December 2014 and November 2024. A total of 29 male patients with HA (all Hemophilia A cases) (mean age: 33.38±8.62 years; range, 20 to 55 years) were included in this study. Exclusion criteria were as follows: (1) incomplete or insufficient clinical data; (2) hepatic or renal dysfunction; (3) pre-existing coagulation disorders or other conditions affecting coagulation; and (4) use of anticoagulants or antiplatelet agents within 14 days prior to admission. A written informed consent was obtained from each patient. The study protocol was approved by the First Affiliated Hospital of Guangzhou University of Chinese Medicine Ethics Committee (Date: 21.11.2025, No: K-2025-195). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All surgeries were performed by the same senior surgical team. A standardized, multidisciplinary PBM protocol was implemented, involving orthopedic surgeons, anesthesiologists, hematologists, nurses, and laboratory specialists. Real-time clinical decision-making was facilitated via dedicated instant messaging platforms to ensure dynamic assessment and continuity of care.

Preoperative evaluation included complete blood count, coagulation profiles, and baseline factor VIII coagulant activity (FVIII:C). Inhibitor screening was performed for all patients to assess the risk of factor resistance. A FVIII sensitivity test was conducted by administering a 15 IU/kg test dose of FVIII concentrate. Plasma FVIII:C levels were measured 15 min and 2 h post-infusion. The individual dose required to reach the target activity was calculated using the following formula: FVIII dose (IU) = body weight (kg) × [target FVIII:C (%) - baseline FVIII:C (%)] ÷ 2.

Two hours prior to surgery, FVIII was supplemented to achieve a target FVIII:C > 80%. Clotting factor concentrates (CFCs) and bypassing agents (e.g., activated prothrombin complex concentrate [aPCC], recombinant human factor VIIa [rhFVIIa]) were prepared as rescue therapies.

General anesthesia was the preferred technique to avoid the risk of neuraxial hematoma associated with spinal or epidural anesthesia. Anesthesia was induced with sufentanil (0.3 μg/kg), propofol (1.5-2 mg/kg), and vecuronium (0.1 mg/kg). To minimize airway trauma and potential bleeding, intubation was performed using a reinforced flexible endotracheal tube guided by an electronic flexible bronchoscope by senior anesthesiologists. Anesthesia was maintained with sevoflurane (2%), propofol (1-2 mg/kg/h), and remifentanil (0.05-0.1 μg/kg/min).

Intravenous tranexamic acid (TXA, 15 mg/kg) and desmopressin (DDAVP, 0.3 μg/kg) were administered 30 min before the skin incision. For patients undergoing simultaneous double TJA, intraoperative cell salvage was prepared preoperatively to minimize the requirement for allogeneic blood transfusion. Controlled hypotension and restrictive fluid management were employed to minimize clotting factor dilution. Forced-air warming was used to maintain normothermia. A pneumatic tourniquet was routinely used during TKA and released prior to wound closure to ensure adequate hemostasis. The FVIII:C levels were monitored every 1.0 to 1.5 h intraoperatively, maintaining a target range of 80 to 100%. In cases of TKA, an additional FVIII bolus was given 15 min before tourniquet release to ensure hemostatic efficacy during the reperfusion phase.

Postoperative recovery was facilitated by a comprehensive multimodal analgesia strategy and rigorous clinical monitoring. Specifically, patients received ultrasound-guided single-shot adductor canal block (15 mL of 0.2% ropivacaine) for TKA or fascia iliaca compartment block (20 mL of 0.2% ropivacaine) for THA. An intravenous cyclooxygenase-2 (COX-2) inhibitor (e.g., parecoxib 40 mg) was administered prior to wound closure, supplemented by the initiation of a patient-controlled intravenous analgesia (PCIA)

TABLE I
Preoperative baseline characteristics of patients with hemophilia

	Total (n = 29)					STJA (n = 18)					DTJA (n = 11)					
Variables	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			33.38±8.62					33.28±8.32					33.55±9.50			0.937
Sex																
Male	29	100				18	100				11	100				-
Weight (kg)			61.10±10.45					61.53±10.22					60.41±11.30			0.785
BMI (kg/m^2)			21.57±3.56					21.82±3.54					21.16±3.73			0.636
Surgical site																0.037
Knee	14	48.3				11	61.1				3	27.3				
Hip	12	41.4				7	38.9				5	45.4				
Knee + Hip	3	10.3				0	0				3	27.3				
Severity of hemophilia																0.531
Mild	10	34.5				5	27.8				5	45.5				
Moderate	17	58.6				12	66.7				5	45.5				
Severe	2	6.9				1	5.6				1	9.1				
FIII:C at admission (%)				2.50	1.75-7.70				2.50	1.78-5.55				4.60	1.70-8.90	0.642
FIII inhibitor level (BU/mL)				0	0-0.25				0	0-0.23				0	0-0.50	0.947
Preoperative laboratory data*																
Hb			147.24±14.21					147.22±12.57					147.27±17.23			0.993
Hct			0.45±0.04					0.45±0.04					0.45±0.05			0.945
PLT			258.83±56.62					259±60.65					230±40.10			0.061
PT			11.53±0.80					11.47±0.72					11.62±0.95			0.643
APTT			29.49±3.06					29.07±2.79					30.18±3.49			0.353
INR			0.95±0.07					0.94±0.06					0.96±0.08			0.553
FIB			2.75±0.81					2.84±0.58					2.60±1.10			0.453

STJA, single total joint arthroplasty; DTJA, double total joint arthroplasty; SD, standard deviation; BMI, body mass index; FIII:C, factor VIII coagulant activity; Hb, hemoglobin; Hct, hematocrit; PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, Fibrinogen; * Data were the results of the last test before the operation.

TABLE II
Perioperative clinical outcomes of patients with hemophilia A

Variables	Total (n = 29)				STJA (n = 18)				DTJA (n = 11)				
	n	%	Mean±SD	Median	Min - Max	n	%	Mean±SD	Median	Min - Max	n	%	Mean±SD	Median	Min - Max	*p*
Length of hospital stay (day)				23.0	19.0 - 31.0				24.0	18.5 - 35.0				22.0	19.0 - 27.0	0.674
Operation time (min)				122.0	91.0 - 182.5				107.5	73.5 - 150.0				170.0	110.0 - 205.0	0.055
Total FVIII consumption (IU)				31300	25500 - 42000				32200	25500 - 40600				31300	24200 - 45600	0.947
Total blood loss (mL)				630.52	470.95 - 939.64				501.74	394.23 - 677.04				799.00	706.79 - 1664.90	0.002
Intraoperative RBC transfusion	11	37.9				4	22.2				7	63.6				0.048
Postoperative RBC transfusion	4	13.8				1	5.6				3	27.3				0.139
Hb change at postoperative Day 5 (g/L)			–41.83±22.81					–34.72±23.20					–53.45±17.37			0.029
Perioperative complications																
Inhibitor development	0	0				0	0				0	0				-
Hemorrhage	0	0				0	0				0	0				-
Venous thromboembolism	0	0				0	0				0	0				-
Reoperation	0	0				0	0				0	0				-

STJA, single total joint arthroplasty; DTJA, double total joint arthroplasty; SD, standard deviation; RBC, red blood cell; Hb, hemoglobin.

system for the immediate postoperative period. Throughout the recovery phase, complete blood counts, coagulation profiles, and FVIII:C levels were monitored at regular intervals. These longitudinal laboratory findings allowed for the dynamic and individualized titration of CFCs doses, ensuring that hemostatic stability was maintained while accommodating the specific metabolic response of each patient.

The primary outcome was TBL, calculated using the Mercuriali's formula.[7] Total blood volume (TBV) was first estimated using the Nadler formula:[8] $TBV = 0.367 \times height^3\ (m) + 0.032 \times weight\ (kg) + 0.604$. The TBL was then calculated as: TBL = TBV × (Hctpre - Hctpost_day 5) + volume of transfused RBCs (mL).

Secondary outcomes included operation time, length of hospital stay (LOS), perioperative Hb fluctuations, and the incidence of complications.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 27.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess data normality. Normally distributed data were presented in mean ± standard deviation (SD), while non-normally distributed data were presented in median and interquartile range (IQR). Categorical variables were presented in number and frequency. Inter-group comparisons were performed using independent samples t-tests or Mann-Whitney U tests. Categorical data were analyzed using the Fisher exact test. A two-sided p value of < 0.05 was considered statistically significant.

RESULTS

Of a total of 29 male HA patients, 18 underwent single TJA (STJA), and 11 underwent simultaneous double TJA (DTJA). Baseline characteristics, including body mass index (BMI), hemophilia severity, baseline FVIII:C level, and FVIII inhibitor titers, preoperative hemoglobin (Hb), hematocrit (Hct), platelet count (PLT) and coagulation profiles, are summarized in Table I. No statistically significant differences were observed in baseline characteristics between the STJA and DTJA groups ($p > 0.05$).

For the entire cohort, the median TBL was 630.52 (IQR: 470.95 to 936.64) mL, and the mean decrease in Hb on postoperative Day 5 was 41.83±22.81 g/L. The median operative time was 122.0 (IQR: 91.0 to 182.5) min, and the median LOS (LOS) was 23.0 (IQR: 19.0

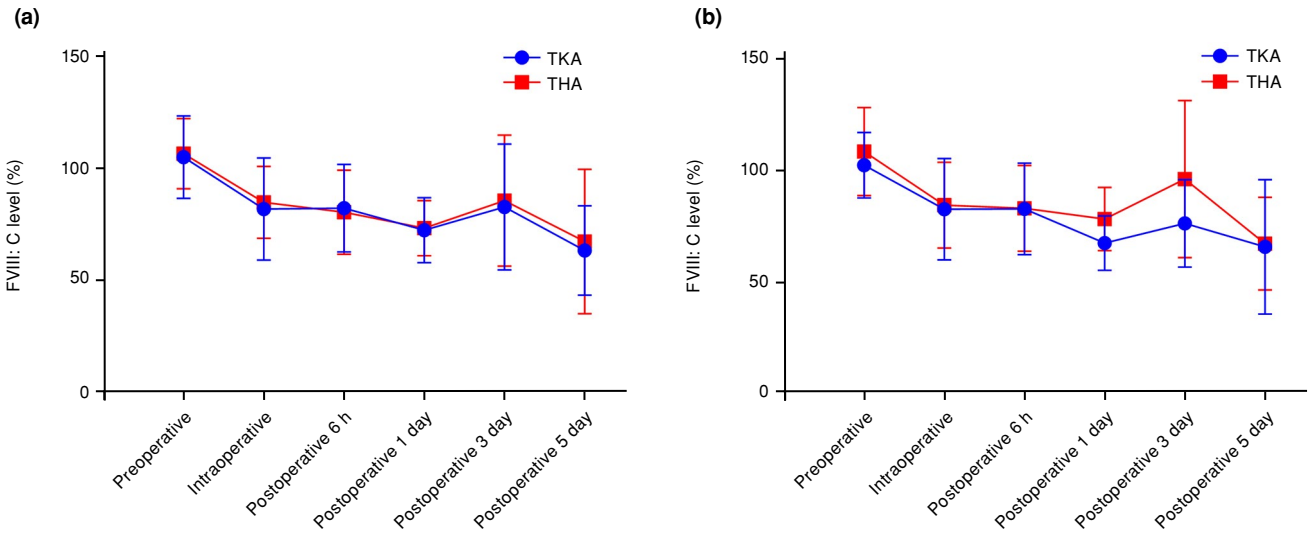

FIGURE 1. Perioperative fluctuations of FVIII:C levels in patients with hemophilia A. **(a)** patients undergoing single TJA and simultaneous double TJA; **(b)** patients undergoing TKA and THA.
TJA, total joint arthroplasty; TKA, total knee arthroplasty; THA, total hip arthroplasty.

to 31.0) days. Detailed outcomes are presented in Table II.

Patients undergoing DTJA experienced significantly higher TBL and a greater reduction in Hb levels on postoperative Day 5 compared to those undergoing STJA ($p < 0.05$, Table II). Consequently, the requirement for intraoperative RBC transfusion was significantly higher in the DTJA group ($p < 0.05$). The perioperative fluctuations of FVIII:C for both groups are illustrated in Figure 1a, demonstrating that target factor levels were consistently maintained across both cohorts.

A subgroup analysis was performed between patients undergoing TKA (n = 14) and THA (n = 12). There were no significant differences in preoperative baseline characteristics between these two subgroups ($p > 0.05$, Table III). Notably, patients in the THA group had a significantly shorter operation time and LOS compared to the TKA group ($p < 0.05$, Table IV). Furthermore, total FVIII consumption was significantly lower in the THA group ($p < 0.05$). However, no significant differences were observed in TBL or the Hb drop on postoperative Day 5 between the TKA and THA groups ($p > 0.05$, Table IV). The perioperative FVIII:C trends for these subgroups are shown in Figure 1b.

DISCUSSION

In the present study, we evaluated the efficacy and safety of a comprehensive, multidisciplinary PBM protocol in patients with Hemophilia A undergoing TJA. Our study results demonstrated that a structured, multidisciplinary PBM protocol could achieve surgical outcomes in patients with hemophilia compared to the general population.

Hemophilia A is a rare X-linked recessive disorder characterized by a congenital deficiency of FVIII. Recurrent intra-articular hemorrhage leads to HA, which severely impairs joint function.[9,10] For end-stage HA, TJA is effective, but carries a high hemorrhagic risk. In our cohort, the median TBL was 630.52 mL. Specifically, the TBL for TKA and THA was 591.28 mL and 591.24 mL, respectively. These values are notably consistent with reported blood loss in non-hemophilic populations undergoing TJA[11,12] and are lower than results reported in several other hemophilic case series[13,14] This discrepancy suggests that our systematic PBM strategy effectively compensates for the underlying coagulopathy, normalizing the surgical risk profile of these patients.

Hemophilia often affects multiple joints. In our study, 11 patients underwent simultaneous double joint replacement. While double-joint procedures were associated with higher TBL and transfusion requirements compared to single-joint procedures, the loss was not two-fold, and there were no significant differences in LOS or total factor consumption. The excellent outcomes may be attributed to the relatively young age and

TABLE III

Preoperative baseline characteristics of patients undergoing TKA and THA

	TKA (n = 14)					THA (n = 12)					
Variables	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			30.64±6.05					36.67±10.50			0.080
Sex											
Male	14	100				12	100				-
Weight (kg)			61.93±10.71					58.42±8.11			0.362
BMI (kg/m^2)			21.68±3.66					21.22±3.49			0.751
Number of joint replaced											0.401
Single joint	11	78.6				7	58.3				
Double joints	3	21.4				5	41.7				
Severity of hemophilia											0.361
Mild	5	35.7				4	33.3				
Moderate	7	50.0				8	66.7				
Severe	2	14.3				0	0				
FVIII:C at admission (%)				2.70	1.78-7.63				2.60	1.75-8.25	
FVIII inhibitor level (BU/mL)				0	0-0.30				0	0-0.15	
Preoperative laboratory data*											
Hb			143.86±17.12					149.67±11.55			0.329
Hct			0.44±0.05					0.45±0.04			0.575
PT			11.67±0.97					11.38±0.61			0.383
APTT			29.87±3.48					28.93±2.09			0.423
INR			0.96±0.08					0.94±0.05			0.668
FIB			2.70±0.90					2.85±0.71			0.630

TKA, total knee arthroplasty; THA, total hip arthroplasty; SD, standard deviation; BMI, body mass index; FVIII:C, factor VIII coagulant activity; Hb, hemoglobin; Hct, hematocrit; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, Fibrinogen; * Data were the results of the last test before the operation.

high baseline Hb levels (147.24±14.21 g/L) of our patients. Our findings suggest that with rigorous factor management, simultaneous double TJA is an efficient and cost-effective strategy for hemophilic patients with high physiological reserves.

Patients with hemophilia undergoing TKA or THA revealed distinct perioperative profiles. Of note, TKA usually requires longer operative time than THA due to more complex procedure and soft-tissue balancing. Postoperatively, patients undergoing TKA often require in-hospital rehabilitation to achieve functional milestones, such as continuous passive motion, which may contribute to prolonged hospitalization.[15] Longer hospital stays are associated with increased factor VIII consumption. Moreover, early and intensive knee flexion-extension exercises after TKA may increase the risk of intra-articular bleeding, necessitating longer duration and higher-dose coagulation factor coverage.[16] In contrast, postoperative rehabilitation after THA primarily emphasizes early weight-bearing ambulation, which may exert less direct impact on local bleeding risk.

Individualized FVIII replacement remains the cornerstone of hemophilic PBM. Following the World Federation of Hemophilia (WFH) guidelines, we targeted FVIII:C levels of > 80% preoperatively and 80 to 100% intraoperatively, followed by a phased tapering to 60 to 80% on postoperative Days 1-3, 40 to 60% on Days 4-6, and 30 to 50% on Days 7-14.[17] The FVIII:C levels were maintained within these recommended ranges. A key feature of our protocol was the preoperative FVIII sensitivity test, which allowed us to predict individual response and tailor doses. By maintaining FVIII:C between 80 and 100% intraoperatively through frequent monitoring (every 1 to 2 h), we minimized the risk of breakthrough bleeding and avoided the risks and costs associated with excessive factor replacement. This dynamic titration is crucial, as factor clearance can accelerate during the stress of major surgery.

In contrast to some earlier domestic consensuses that recommended hemodilution,[5] we advocate for a restrictive fluid strategy. Excessive crystalloid infusion may lead to dilutional coagulopathy, further reducing already fragile factor levels. Regarding controlled hypotension, while some argue it may mask surgical bleeding points,[18] we maintained blood pressure at a "low to normal" range, ensuring it returned to baseline before wound closure to allow for meticulous hemostasis.

TABLE IV
Perioperative outcomes between TKA and THA

Variables	TKA (n = 14)				THA (n = 12)				*p*
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	
Length of hospital stay (days)				25.5	22.8 - 37.3				19.0	14.3 - 22.8	0.002
Operation time (min)				151.5	110.0 - 212.8				84.5	70.0 - 141.50	0.008
Total FVIII consumption (IU)				334500	29625 - 40600				25800	22925 - 33000	0.036
Total blood loss (mL)				591.28	474.33 - 788.43				591.24	427.32 - 1210.33	0.860
Intraoperative RBC transfusion	4	28.6				5	41.7				0.683
Postoperative RBC transfusion	2	14.3				0	0				0.483
Hb change at postoperative Day 5 (g/L)			–33.07±22.27					–46.92±22.19			0.127

TKA, total knee arthroplasty; THA, total hip arthroplasty; SD, standard deviation; RBC, red blood cell; Hb, hemoglobin.

Furthermore, we emphasized the reduction of non-iatrogenic blood loss. Repeated venipuncture and catheterization may contribute significantly to TBL. In our center, senior anesthesiologists used ultrasound-guided techniques to ensure first pass success for all invasive procedures and cell salvage strategy was adopted when clinically indicated.

The administration of TXA and DDAVP was instrumental in our protocol. It is well-established that TXA can stabilize fibrin clots,[19] although we remain cautious with aPCC in Hemophilia B patients due to thrombotic risks. For patients with mild-to-moderate Hemophilia A, preoperative DDAVP effectively boosted endogenous FVIII levels, achieving the purpose of preventing and controlling bleeding.[20]

Effective postoperative analgesia can facilitate early mobilization and mitigates various complications, such as postoperative nausea and vomiting.[21] The safety of regional anesthesia in hemophilic patients remains a subject of ongoing debated.[22] Our experience suggests that once FVIII:C is normalized through target replacement therapy, ultrasound-guided nerve blocks performed by experienced anesthesiologists are safe and superior for postoperative recovery. Our multimodal analgesia approach, combining nerve blocks, local infiltration, and PCIA, yielded excellent pain control without any incidence of hematoma or infectious complications.

The presence of FVIII inhibitors remains a formidable challenge in hemophilic surgery. In our cohort, two patients with low-titer inhibitors (0.7 and 1.8 BU/mL) were successfully managed using standardized factor replacement. For high-titer cases, we recommend bypassing agents such as rhFVIIa or sequential therapy with aPCC, as suggested by the Chinese guideline.[6]

Notably, several patients experienced significant postoperative Hb declines despite controlled intraoperative bleeding, which was consistent with the patterns of hidden blood loss typical in major orthopedic surgery.[23,24] Therefore, longitudinal Hb monitoring is essential to accurately assess TBL. Nevertheless, our PBM strategy was generally safe. No replacement-related complications were observed, including inhibitor development, anaphylaxis, or venous thromboembolism.

Nonetheless, this study has several limitations. First, the single-center, retrospective design and relatively small sample size may limit the generalizability of the findings. In addition, the study predominantly included patients with mild-to-moderate hemophilia and low inhibitor titers, which may not fully represent patients with more severe disease. Second, the absence of a control group precludes causal inference and prevents the assessment of the independent effectiveness of individual components of the PBM protocol. However, given the rarity of hemophilia A and the ethical necessity of providing optimal hemostatic care, establishing a control group (without such management) was not feasible. As a result, the observed outcomes should be interpreted as the combined effect of a comprehensive management strategy rather than attributable to any single intervention. Future multi-center, prospective studies with appropriate control groups are warranted to further validate and refine these perioperative management strategies.

In conclusion, the management of hemophilic patients undergoing TKA or THA requires a meticulously coordinated, multidisciplinary approach. By combining individualized factor replacement, restrictive fluid management, ultrasound-guided anesthetic techniques, and multimodal analgesia, the high hemorrhagic risk associated with hemophilia can be effectively mitigated, ensuring surgical safety and enhancing patient recovery.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: M.P., S.L.: Conceived and designed the study, performed data analysis, and wrote the original draft; X.W.X Was responsible for data collection and literature review; W.M.: Provided materials and supplementary analysis; Y.L., X.W.: Contributed to reference preparation; W.M., Y.L.: Provided critical intellectual input and revised the manuscript; Y.L.: Supervised the project. All authors have read and approved the final version of the manuscript.

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