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Surgical Procedures Requiring Hospitalization and Perioperative Management for Patients with Hereditary Bleeding Disorders

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Background: Hemophilia requires a lifetime care for bleeding control and complications. Although patients diagnosed with hemophilia receive factor replacement, they also experience a variety of medical problems as they age. Elective surgery can be performed through appropriate factor replacement during and after surgery. However, for patients with inhibitors, this remains a problem to be overcome.

Methods: Patients treated for congenital bleeding disorders between 2008 and 2021 were enrolled in this study. The patients were classified according to the type, severity, and presence of inhibitors. The patients underwent planned coagulation factor replacement depending on the type of surgery.

Results: A total of 232 patients treated for congenital bleeding disorders were enrolled. Among them hemophilia A was most prevalent, followed by hemophilia B. In total, 78 of the patients underwent surgery, including 31 major and 55 minor surgeries. Orthopedic surgery was the most common surgery, and patients with inhibitors had significantly more postoperative hospitalization days. Nine patients were incidentally diagnosed. Twelve patients with hemophilia with inhibitors underwent surgery, and 6 of them experienced post-operative complications.

Conclusion: Proper surgical planning and monitoring with a multidisciplinary team will be required for appropriate perioperative management of patients with hemophilia, especially in patients with inhibitor and elderly hemophilia patients.

Key Words: Hemophilia A, Hemophilia B, Surgery, Inhibitors

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Introduction

Congenital bleeding disorder is a rare disease caused by a deficiency or dysfunction of coagulation proteins and can occur sporadically or hereditarily. The prevalence of hemophilia A and B is 1 in 5,000 and 30,000 males, respectively [1-4]. Factor VII deficiency is the most common of the rare coagulation disorders, with a prevalence of 1 in 300,000-1 in 500,000 people [5]. In Korea, the age-standardized incidence rates of hemophilia A and B have been estimated as 1.78-3.15/100,000 and 0.31-0.51/100,000, respectively [6].

Hemophilia, a chronic condition, requires lifetime care for bleeding episodes and complications. Secondary prevention of patients with hemophilia (PWH) has been possible since the 1970s, resulting in fewer complications from bleeding episodes. In fact, plasma-derived factors and recombinant factors for hemophilia A and B were developed in the 20th century, which enabled the reduc-

tion of blood-born infections [1,7]. Thus, life expectancy of PWH has been extended because of safe and effective bleeding prevention. As a consequence of aging, elective surgery and care for elderly PWH are emerging areas of importance [8,9].

Major surgeries include arthroplasty, open reduction, internal fixation, abdominal surgery, thoracic surgery, neurological surgery, and any type of "-ectomy" or "-otomy". Minor surgery includes insertion/replacement/removal of central venous access device, biopsy, circumcision, and dental procedures.

Since the advent of the low-dose protocol for invasive procedures in the 1990s, efforts have been made to prevent bleeding from invasive procedures and surgery [10]. The World Federation of Hemophilia (WFH) guidelines for the management of hemophilia recommend factor replacement schemes using standard half-life products, taking into account plasma factor peak levels and duration [11]. Extended half-life (EHL) agents that reduce the number and consumption of infusions are also available for perioperative hemostatic management of surgery [12]. Administration of the recently developed non-factor prophylaxis allows surgeons to safely perform minor surgery without additional factor replacement and major surgery with additional factor replacement [13].

The development of factor inhibitors is the most significant and costly complication in PWH, and is problematic even in surgical procedures [14]. Immune tolerance induction or bypassing agents, including activated prothrombin complex concentrates (aPCC) and activated factor VII (FVIIa), have demonstrated efficacy in controlling bleeding in PWH with inhibitors. As an alternative treatment, the non-factor agent, emicizumab, has recently been shown to effectively control bleeding in the perioperative period in PWH with inhibitors [13].

Therefore, in this single-center study, we investigated the prevalence and characteristics of coagulopathy at our hospital. In addition, we evaluated the types of surgery, post-operative complications, and duration of hospitalization for surgery as outcomes to confirm the effectiveness of the management and prophylaxis for PWH.

Materials and Methods

1) Patient population

Patients with coagulation factor deficiency who were treated according to the WFH guidelines between January 2008 and December 2021 in the Department of Pediatric Hematology & Oncology at Yonsei Cancer Center were enrolled in this study. We classified the patients according to their diagnosis of hemophilia A (HA), B (HB), C (HC), or factor VII deficiency (F7d). Clinical data, including the type of surgery, coagulation factor consumption, and duration of hospitalization for surgery, were retrieved from electronic medical records. This study was approved by the Institutional Review Board (IRB) of Yonsei University Health System Clinical Trials Center (IRB No. 4-2022-0915).

2) Definition

Surgery for PWH is categorized as either major or minor based on the expected intensity of the surgical outcome as well as the surgical and post-operative durations for hemostasis [15].

We classified the severity of hemophilia according to the coagulation factor deficiency; severe hemophilia was defined by coagulation factor deficiency less than 1% of the normal range, moderate as less than 1-5%, and mild as less than 5-40% [16]. Patients with a Bethesda titer of >0.6 Bethesda units (BU) for FVIII and ≥ 0.3 BU for FIX were considered positive for an inhibitor [16].

3) Perioperative treatment

Plasma-derived or recombinant factors were administered to patients with hemophilia A and B. Patients were given coagulation factor replacement with a peak target level of 80-100 IU/dL for major surgery and 50-80 IU/dL for minor surgery for hemophilia A or 60-80 IU/dL for hemophilia B at the start of the surgery [16,17]. Factor replacement was administered for at least seven days to those undergoing major surgeries and for 1-5 days to those undergoing minor surgery [16,17]. For PWH with an inhibitor, FVIIa [NovoSeven® (Novo Nordisk A/s, Bagsvaerd, Denmark)] or factor 8 inhibitor bypassing ac-

tivity [FEIBA® (Baxter AG, Vienna, Austria)] was administered under close clinical follow-up for hemostasis. Patients with hemophilia C received fresh frozen plasma (FFP). For patients with factor VII disease, FVIIa or FFP was used for perioperative management.

4) Statistical analysis

Descriptive analyses were used to evaluate patient demographics, and numerical data are presented as median and interquartile ranges. For the statistical test, Fisher's exact test was used to analyze the parametric variables, and the Mann-Whitney U and Kruskal-Wallis tests were used for non-parametric variables. All statistical analyses were performed using IBM SPSS version 23.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA) and R statistical software version 4.1.0 (Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 232 patients with congenital bleeding disorders were treated during the study period. By type, HA was the most common (180, 77.6%), followed by HB (40, 17.2%) (Table 1). Fourteen (6.0%) patients were female, comprising 10 mild HA or HB carriers, 2 HC carriers, and 2 F7d carriers. Regarding severity, 129/180 (71.7%) HA and 21/40 (52.5%) HB cases were of the severe type. The number of patients with HA with inhibitors (HAI) and those with HB with inhibitors was 16/180 (8.9%) and 6/40 (15.0%), respectively.

Of those treated, 78 (33.2%) underwent surgery: 67/180 (37.2%) with HA, 11/40 (27.5%) with HB, 3 with HC, and 3 with F7d. A total of 86 surgeries and procedures were performed among the patients who participated in the study, among which 31 were major cases and 55 were minor cases (Supplementary Table 1). The most common types of major surgery for patients with HA and HB with and without inhibitors were orthopedic surgery (18/28, 64.3%) and particularly arthroplasty (12/18, 66.7%). There was no difference in the type of surgery according to the type of hemophilia; however, patients with inhibitors (PWI) tended to have more dental surgical procedures than those with HA or HB (Table 2). Hematoma was the most common postoperative complication of

Table 1. Distribution of hereditary bleeding disorders

Diseases	Total		Surgery[a]		Age (year)[b]
	N	%	n[a]	%[a]	Median (IQR)[b]
Hemophilia A					
Total	180	77.6	67	79.8	36.5 (21.0-46.0)
Severe	129	55.6	37	44.0	37.0 (24.0-45.0)
Moderate	17	7.3	11	13.1	27.0 (14.5-47.5)
Mild	18	7.8	3	3.6	30.0 (24.5-38.0)
Female (carrier)[c]	7	3.0	2	2.4	42.5 (40.8-44.3)
With inhibitor	16	6.9	16	19.0	33.0 (1.8-46.0)
Hemophilia B					
Total	40	17.2	11	13.1	20.0 (5.0-30.0)
Severe	21	9.1	2	2.4	20.0 (10.5-33.5)
Moderate	8	3.4	3	3.6	14.0 (13.0-36.5)
Mild	5	2.2	1	1.2	29.0 (28.5-29.5)
Female (carrier)[c]	3	1.3	1	1.2	30.0 (30.0-30.0)
With inhibitor	6	2.6	5	6.0	5.0 (5.0-30.0)
Hemophilia C	6	2.6	3	3.6	42.0 (26.5-51.0)
Factor VII deficiency	6	2.6	3	3.6	6.0 (5.5-7.0)
Total	232	100	84	36.2	

[a]Proportion of patients who underwent surgery for each hemophilia among all patients who underwent surgery. [b]Age distribution of the patients who underwent surgery. [c]All carriers were mild.

Table 2. Types of surgeries and procedures according to the type of hemophilia and presence of inhibitors

Surgeries & procedures	HA[a] (n=51)		HB[b] (n=6)		PWI[c] (n=21)		*P*-value[d]	Total (n=78)	
	n	%	n	%	n	%		n	%
Major (n=28)									
OS	12	66.7	2	11.1	4	22.2	0.26	18	64.3
GS	4	100	0	-	0	-	0.38	4	14.3
NS	2	66.7	0	-	1	33.3	0.35	3	10.7
Minor (n=50)									
DEN	6	50.0	0	-	6	50.0	0.07	12	24.0
URO	2	40.0	1	20.0	2	40.0	0.40	5	10.0
ENT	3	100	0	-	0	-	0.47	3	6.0

[a]Hemophilia A without inhibitor. [b]Hemophilia B without inhibitor. [c]All patients with inhibitor in both hemophilia A and hemophilia B. [d]*P*-value through the chi-square test.
HOD, days of hospitalization; HA, hemophilia A; HB, hemophilia B; PWI, patients with inhibitors; OS, orthopedic surgery; GS, general surgery; NS, neurosurgery; DEN, dental surgery; ENT, ENT surgery; URO, urological surgery.

Table 3. Days of hospitalization according to the type of hemophilia and surgery

Surgeries & procedures	HA (n=51) HOD[a]	HB (n=6) HOD[a]	PWI (n=21) HOD[a]	*P*-value[b]	Total (n=78) HOD[a]
Major (n=28)	17.5 (13.8-20.5)	24.5 (22.8-26.3)	43.0 (32-89.25)	0.02[c]	20.0 (16.0-27.0)
OS (n=18)	19.0 (5.5-44.8)	-	-	-	19.0 (5.5-44.8)
GS (n=4)					
NS (n=3)	42.5 (25.8-59.3)	-	19.0 (19.0-19.0)	0.40	19.0 (14.0-47.5)
Minor (n=50)	1.0 (1.0-1.0)	-	4.0 (2.5-4.75)	0.02[c]	1.0 (1.0-4.0)
DEN (n=8)					
URO (n=5)	9.5 (7.8-11.3)	5.0 (5.0-5.0)	10.0 (9.5-10.5)	0.36	9.0 (6.0-11.0)
ENT (n=3)	6.0 (5.0-7.0)	-	-	-	6 (5.0-7.0)

[a]Median value and inter-quartile range of HOD (days). [b]*P*-value through Kruskal-Wallis test. [c]*P*-value <0.05.
HOD, days of hospitalization; HA, hemophilia A; HB, hemophilia B; PWI, patients with inhibitors; OS, orthopedic surgery; GS, general surgery; NS, neurosurgery; DEN, dental surgery; ENT, ENT surgery; URO, urological surgery.

hemophilia. In addition, there were infection, wound dehiscence, hematochezia, hematuria, and severe complications such as sepsis and cerebral hemorrhage.

Moreover, PWI had a longer hospital stay following orthopedic surgery than that of those with HA or HB (Table 3). The most common minor surgeries or procedures were endoscopic procedures (16/52, 32.8%), followed by dental surgery (13/52, 25.0%) in both HA and HB. More PWI were admitted and had a longer hospitalization stay for dental treatment than that of those with hemophilia A or B (Table 2, 3). Patient who underwent major surgery required longer hospital stays than those who underwent minor surgery (17.5 days vs. 3.0 days, $P<0.001$); however, there was no difference in the number of days hospitalized by hemophilia type (Supplementary Table 2).

Minor surgery was performed significantly more frequently in patients younger than 20 years than in patients older than 20 years old ($P=0.02$) (Supplementary Table 3). All 4 of the patients who underwent neurosurgery were younger than 5 years, and 3 of them were craniotomy or ventriculoperitoneal shunt due to complications of intracranial hemorrhage. There were 2 cases of orthopedic surgery performed in patients under the age of 10 years for compartment syndrome and fibrous dysplasia. Arthroplasty and joint replacement were performed in patients since their late twenties. Two patients in their sixties underwent cancer surgeries for prostate cancer and colon cancer.

Twelve PWI underwent surgeries (6 major and 15 minor), and 6 of them had postoperative complications

Table 4. Types of surgery and complications in patients with hemophilia and inhibitors

Case	Dx	Sex	Age	Surgery	Factor replacement	Factor consumption	HOD	Complication
1	HA	M	1	VP shunt	Anti-Inhibitor coagulant complex	FEIBA 179.1 unit/kg/d	19	None
			1	Chemoport insertion#1	Factor VII	Novoseven 55.6 KIU/kg/d	21	Hematoma
			1	Chemoport insertion#2	Anti-Inhibitor coagulant complex	FEIBA 179.1 unit/kg/d	6	None
			5	Extropia repair	None	None	1	None
2	HA	M	1	Primary closure due to laceration	Factor VII	Novoseven 12.2 KIU/kg/d	6	Sustained bleeding
3	HA	M	2	Lingual frenectomy	None	None	1	None
4	HA	M	29	Total knee arthroplasty	Factor VII	Novoseven 56.0 KIU/kg/d → FEIBA 203.1 unit/kg/d	23	Sustained bleeding, delayed wound healing
			24	Surgical extraction	Anti-Inhibitor coagulant complex	FEIBA 195.3 unit/kg/d	4	None
5	HA	M	37	Primary closure due to skin defect	Factor VII	Novoseven 4.5 KIU/kg/d	2	None
6	HA	M	39	Cystoscopy with biopsy	Factor VII	Novoseven 53.8 KIU/kg/d	9	None
			42	Surgical extraction	Factor VII	Novoseven 51.2 KIU/kg/d	7	None
			46	Pulp extirpation	Factor VII	Novoseven 37.4 KIU/kg/d	4	None
7	HA	M	46	Total knee arthroplasty	Factor VII	Novoseven 41.3 KIU/kg/d	204	Hematoma, wound dehiscence
8	HA	M	48	Surgical extraction	Factor VII	Novoseven 13.2 KIU/kg/d	2	None
			49	Colonoscopy with polypectomy	Factor VII	Novoseven 5.4 KIU/kg/d	1	None
			47	Cystoscopy	Factor VII	Novoseven 29.4 KU/kg/d	11	None
9	HB	M	3	Chemoport removal	Factor VII	Novoseven 46.5 KIU/kg/d	6	None
10	HB	M	5	Tendon lengthening	Anti-Inhibitor coagulant complex	FEIBA 188 unit/kg/d	51	Wound dehiscence
			5	Chemoport removal & insertion	Anti-Inhibitor coagulant complex	FEIBA 188 unit/kg/d	25	None
11	HB	M	30	Cyst enucleation	Factor VII	Novoseven 49.0 KIU/kg/d → FEIBA 204.4 unit/kg/d	5	Sustained bleeding
12	HB	M	37	Achilles tendon tenotomy	Factor VII	Novoseven 57.9 KIU/kg/d	35	None

Dx, diagnosis; HOD, days of hospitalization; HA, hemophilia A; HB, hemophilia B; VP-shunt, ventriculoperitoneal shunt.

(Table 4). Complications included postoperative bleeding or delayed wound healing, resulting in dehiscence or infection. PWI showed more complications, and in the case of dental treatment, a longer hospitalization was required due to complete hemostasis after the procedure (Table 3).

Nine patients were newly diagnosed with hemophilia during hematology consultation for the operative procedure, 3 with HA, 2 with HB, 3 with F7d, and 1 with HC (Table 5). All patients were referred to hematologists for high prothrombin time (PT) or activated partial thromboplastin clotting time (aPTT). A 64-year-old male with previously known HA was transferred to our hospital for robot-assisted laparoscopic radical prostatectomy for prostate cancer, and he experienced repeated postoperative bleeding despite FVIII replacement. He was referred for repeated bleeding complications; factor XI deficiency was confirmed, and the diagnosis was amended.

Discussion

In this study, the surgical procedures and hospitalization days for HA and HB were similar. Patients with HB are known to have fewer and less severe clinical symptoms and lower factor consumption for procedures [18] however, in this study, the difference could be overcome by the administration of proper factors during and after surgery. In addition, although minor surgery can be performed in an outpatient setting, PWH with inhibitors require hospitalization for more delicate monitoring of

Table 5. Incidentally diagnosed coagulation factor deficiency during hematology consultation for operative procedures

Sex	Age	Diagnosis	PT (9.2-13.1 sec)	INR (0.89-1.12 INR)	aPTT (26.8-40.6 sec)	Factor level	Surgery
M	0	Hemophilia A	11.9	1.04	139.4	Factor VIII (<1%)	Craniotomy & hematoma evacuation
M	1	Hemophilia B	11.7	1.02	59.6	Factor IX (4.0%)	Mass excision, scalp
M	4	Factor VII deficiency	15.1	1.32	40.5	Factor VII (36.9%)	Osteotomy, open reduction and internal fixation of femur
F	4	Factor VII deficiency	15.7	1.37	32.7	Factor VII (27.1%)	V-tube insertion
M	6	Factor VII deficiency	16.5	1.51	35.4	Factor VII (20.0%)	Frenectomy
M	7	Hemophilia A	11.2	0.98	54.0	Factor VIII (6.1%)	Endoscopic biopsy
M	14	Hemophilia B	17.1	1.52	49.9	Factor IX (8.5%)	Incision and drainage (intramuscular hip abscess)
M	58	Hemophilia A	10.8	0.95	63.6	Factor VIII (4.2%)	Endoscopic biopsy
M	64	Hemophilia C	12.2	1.07	74.7	Factor XI (14.6%)	Laparoscopic radical prostatectomy

PT, prothrombin time; aPTT, activated partial thromboplastin clotting time.

hemostasis. Pediatric PWH require hospitalization for general anesthesia, even for minor surgeries. A multidisciplinary team consisting of experienced professionals is needed to plan surgical procedures for hemophilia [8,16].

Proper management of PWH enables a longer survival period; however, the risk of chronic disease due to recurrent bleeding episodes, infection, or aging increases accordingly. Arthroplasty and synovectomy for PWH are usually performed after the age of 30 years [19]. As PWH age, they may require surgery for chronic health conditions or adult diseases, including cancer surgery [i.e., hepatocellular carcinoma (HCC)], cardiovascular intervention, endoscopic surgery for prostatic hypertrophy, or surgery for cataract [9]. During surgical planning for elderly patients, comorbidity of chronic diseases and blood-borne infectious diseases, such as viral hepatitis and HIV infection, should also be considered. In addition, there is a risk of thrombosis due to immobilization after surgery, and early mobilization is recommended [9,16].

In this study, PWI showed a longer hospitalization duration and more required hospitalization for minor surgical procedures because PWI has the potential to cause life-threatening bleeding [15]. Among those with low-titer inhibitors (<5 BU), hemostasis can be achieved with higher- than- normal doses of factors that overcome the inhibitors, whereas in those with high-titer inhibitors, hemostasis can be achieved with bypassing agents that circumvent the need for factor VIII or IX concentrates [8]. The risk of uncontrolled bleeding remains a serious threat, which leads to increased hospitalization, even for minor surgeries, as well as more postoperative hospitalization days and complications [15]. They require more delicate monitoring of bleeding episodes and proper use of bypassing agents for hemostasis [8,15,16].

The development of newer classes of hemostatic agents has presented PWH new surgical opportunities and challenges. Recombinant EHL factors for hemophilia A and B can reduce the number of factor infusions and total factor consumption during surgery [13]. With the development of non-factor hemostatic agents, such as emicizumab, that is the humanized bispecific monoclonal antibody bridging factors IX and X, concerns about combination treatment with coagulation factors and non-factor agents during surgical procedures are increasing. Emicizumab was shown to be safe and effective in PWH without thrombosis during surgery without aPCC [12,14]. In addition, fitusiran against antithrombin and concizumab against TFPI were proven safe to use without thrombosis during surgery [20,21]. However, additional unknown risks remain regarding the use of combination

treatments. Although there is a lack of reliable laboratory monitoring of the agents, appropriate use of non-factor agents during surgery should be studied further, as they will be an important component of surgical procedures for PWH in the coming decades [12].

Patients over the age of one year who are newly diagnosed hemophilia during the pre-operation consultation usually showed only mild disease because they did not have any significant bleeding episodes except for abnormal coagulation test results. However, the severity of hemophilia in newly diagnosed patients ranges from moderate to severe in PWH younger than one year. Because some PWH may have normal or near-normal PT/aPTT test results, clinical suspicion for hemophilia that considers patient age and previous bleeding episodes should be provided [22]. In addition, when bleeding control is not adequate, even with coagulation factor replacement according to the previous diagnosis, it is necessary to check whether the previous diagnosis is correct [23].

This study has several limitations. Clinical data were obtained from patients with surgical medical records; however, data on the type of minor surgery, such as simple tooth extraction without regular surgical records, could be missing. The factor consumption for each surgical procedure was not retrieved or analyzed. In conclusion, PWI showed difficulty in hemostasis during surgical procedures, and the patterns of surgery changed as the patients aged. New patients can be detected during the surgical consultation. Proper surgical planning with a multidisciplinary team will be required for appropriate perioperative management of PWH in preparation for complicated future conditions in the era of elderly hemophilia patients and the newer classes of hemostatic agents.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.15264/cpho.2022.29.2.52.

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