Clinical analysis of hospitalized patients with hemophilia A: single-hemophilia treatment center experience in Korea over 10 years

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Background
There is lack of data on admitted hemophilia patients in Korea. For this reason, this study was intended to analyze the hospitalization data of hemophilia patients in a regional Hemophilia Treatment Center (HTC) for the first time in Korea.

Methods
In this retrospective study, we surveyed hospitalized patients with Hemophilia A (HA) in a HTC for 14 years. Medical records of these hemophiliacs were reviewed and data regarding demographic characteristics, cause of admissions and their outcomes in each patient were obtained. In addition, the data of admitted days, type and amount of Coagulation factor concentrate (CFC) used, treatments other than CFC infusion during the admission days were also obtained from the medical record of each patient.

Results
A total 107 patients with hemophilia A were admitted during 14 years. Annual rate of admission of patients with HA was 8%. Mean age on admission was 29.63±19.51 years old and mean admission days were 11.28±5.46 days. Most admissions were occurred in severe and moderate hemophilia patients. The most common cause of admission was bleed control followed by surgery and other reasons. With modified WFH CFC supplementation guideline, all the bleeds were successfully controlled and all surgeries were also successfully conducted with less total CFC consumption compared to the consumed dose of other reports.

Conclusion
These results suggest that it is necessary to develop more specified regimens different from WFH guidelines of CFC supplementation for admitted Korean patients with hemophilia A.

Key Words
Hemophilia A, Admitted patient, Analysis, Factor VIII concentrate consumption, Korea

INTRODUCTION

Hemophilia is caused by various mutations of the factor 8 and factor 9 gene located on the X chromosome; thus, the coagulation factor VIII and factor IX activity is reduced [1]. The severity of hemophilia is classified by the level of coagulation factors: > 5.0 IU/dL, mild; 1.0-5.0 IU/dL, moderate; and < 1.0 IU/dL, severe hemophilia [2]. Hemophilia patients experience repeated joint bleeding episodes for their lifetime and arthropathy is the main complication of these repeated joint bleeding episodes, which often require orthopedic surgical management [3-5].

All surgical procedures for hemophilia patient should be conducted with the measures of prevention of excessive bleedings by regularly administering deficient coagulation factor concentrates (CFCs) to these patients, which require admission care. All hemophilia patients are at risk of severe bleedings, which need admission and imminent control of bleedings. Therefore, hospitalization is inevitable for the treatment of serious bleeding control or prevention of bleeding complications in any surgical procedure conducted for
hemophilia patients irrespective of the severity of hemophilia. The treatment of hemophilia is costly mainly due to the high cost of CFCs; therefore, cost-effective guidelines are required for hemophilia treatment, especially for CFC supplementation in admission cases, because of larger amount of CFCs administered to patients compared to CFC supplementation in outpatient care.

However, data are lacking on admitted hemophilia patients in Korea; there is no appropriate national guidance based on clinical experiences on admitted patients with hemophilia in Korea. Therefore, this study analyzed the hospitalization data of hemophilia patients over 10 years in a regional hemophilia treatment center (HTC) for a 1.5-million population in Daejeon province in Korea. This study aimed to characterize a population of admitted patients with hemophilia and to identify states of hemophilia treatment for the patients to pave the way to establish pragmatic national guidelines for the treatment of admitted hemophilia patients in Korea.

**MATERIALS AND METHODS**

**Study subjects and acquisition of needed data**

Patients with hemophilia hospitalized at Eulji university hospital in Korea between January 2004 and December 2018 were included in this retrospective study. This study was conducted only for patients with hemophilia A (HA) because the number of admitted cases of patients with hemophilia B or inhibitor was so small for evaluation.

Overall, 107 HA patients with varied severity defined

| Type of hemorrhage                                           | Hemophilia A                                                                 |
|--------------------------------------------------------------|-------------------------------------------------------------------------------|
|                                                              | Lower- dose practice pattern | Higher- dose practice pattern |
|                                                              | Peak factor level (IU/dL) | Treatment duration (d) | Peak factor level (IU/dL) | Treatment duration (d) |
| Joint                                                        | 10-20 | 1-2<sup>a</sup> | 40-60 | 1-2                      |
| Superficial muscle/no NV compromise (except iliopsoas)       | 10-20 | 2-3<sup>a</sup> | 40-60 | 2-3<sup>a</sup>          |
| Iliopsoas or deep muscle with NV injury or substantial blood loss |                   |                     |                  |                          |
| Initial                                                      | 20-40 | 1-3          | 80-100 | 1-3                      |
| Maintenance                                                  | 10-20 | 3-5<sup>b</sup> | 30-60 | 3-5<sup>b</sup>          |
| Intracranial                                                | 50-80 | 1-3          | 80-100 | 1-7                      |
| Maintenance                                                  | 20-40 | 8-14         | 50     | 8-21                     |
|                                                             | 30-50 | 4-7          | -      | -                        |
| Throat and neck                                             | 30-50 | 1-3          | 80-100 | 1-7                      |
| Maintenance                                                  | 10-20 | 4-7          | 50     | 8-14                     |
| Gastrointestinal                                            | 30-50 | 1-3          | 80-100 | 7-14                     |
| Initial                                                      | 10-20 | 4-7          | 50     |                          |
| Maintenance                                                  | 20-40 | 3-5          | 50     | 3-5                      |
| Deep laceration                                             | 20-40 | 5-7          | 50     | 5-7                      |
| Surgery (major)                                             | 60-80 | 80-100       |       |                          |
| Pre-op                                                      | 30-40 | 1-3          | 60-80  | 1-3                      |
| Post-op<sup>c</sup>                                         | 20-30 | 4-6          | 40-60  | 4-6                      |
|                                                             | 10-20 | 7-14         | 30-50  | 7-14                     |
| Surgery (minor)                                             | 40-80 | 50-80        |       |                          |
| Pre-op                                                      | 20-50 | 1-5          | 30-80  | 1-5                      |

In this table, the desired peak factor levels of CFC replacement shown for treatment of hemorrhages at different anatomical sites represent the ranges in global practice patterns depending on available resources. Importantly, it should be recognized that the goal of such treatment is effective control of bleeding and should be the same everywhere in the world. Lower CFC replacement levels require much closer observation for effectiveness of bleeding control, with a potentially greater chance of requiring additional CFC replacement to achieve the target plasma level as well as the hemostatic and musculoskeletal outcomes.

<sup>a</sup>May be longer if response is inadequate.  
<sup>b</sup>Sometimes longer as secondary prophylaxis during physical therapy.  
<sup>c</sup>The duration of treatment refers to sequential days post-surgery. Type of CFC and patient's response to CFC should be taken into account.  
<sup>d</sup>Depending on procedure; the number of doses would depend on the half-life of the CFC used.

Abbreviations: CFC, clotting factor concentrate; NV, neurovascular.
Clinical analysis of admitted hemophilia patients

by the basal factor VIII level were admitted during the period. Medical records of these hemophiliacs were reviewed and data regarding demographic characteristics and cause of admissions such as control of bleeding and surgeries were obtained for each patient. The severity and type of bleedings, type of operations and their outcomes in each patient were also obtained from the medical records. Additionally, the data of admitted days, type and amount of CFC used, treatments other than CFC infusion during the admission days were also obtained from the medical records of each patient.

Classifications of admission cases according to the cause of admission

The hospitalization cases were classified into 3 groups according to the cause of admission: surgery, bleed control, and other reasons of admission. Patients who were hospitalized for control of bleeding were classified according to the severity of bleeding: severe, moderate, and mild bleeding.

The patients admitted for surgery were classified into orthopedic surgery and other operations because more orthopedic surgeries tend to be performed on hemophilia patients due to the high incidence of arthropathy complications. Each operation was classified into major and minor surgery according to the type of surgery. Major surgery is any invasive operative procedure, in which a more extensive resection is performed and surgery involving a risk to life. Minor surgery is any invasive operative procedure, in which only skin or mucus membranes and connective tissue is resected and surgery involving little risk to life [6-8].

Patient demographics, length of hospital stays, amount and type of CFCs used, and outcome of the admissions were obtained from the medical records of each patient. Additionally, the observed data were compared between cases of severe and non-severe bleeds in the bleed control group.

| Year | N of admitted case | N of admitted patient | Type of hemophilia severity | Mean age on admission (yr) | Mean admission days |
|------|-------------------|-----------------------|----------------------------|----------------------------|--------------------|
| 2018 | 6                 | 6                     | S 4 M 2                    | 20.5                       | 5.83               |
| 2017 | 7                 | 5                     | S 1 M 4                    | 14.57                      | 4.71               |
| 2016 | 10                | 8                     | S 5 M 3                    | 24                         | 11.1               |
| 2015 | 5                 | 5                     | S 2 M 3                    | 27.8                       | 8.8                |
| 2014 | 12                | 10                    | S 7 M 3                    | 28.17                      | 9.25               |
| 2013 | 9                 | 7                     | S 5 M 2                    | 33.67                      | 21.11              |
| 2012 | 11                | 8                     | S 6 M 2                    | 29.55                      | 24.63              |
| 2011 | 12                | 11                    | S 9 M 2                    | 22.58                      | 6                  |
| 2010 | 10                | 10                    | S 7 M 3                    | 25.82                      | 11.18              |
| 2009 | 8                 | 7                     | S 4 M 2                    | 23.5                       | 12.38              |
| 2008 | 12                | 6                     | S 3 M 3                    | 49.33                      | 13.58              |
| 2007 | 8                 | 5                     | S 2 M 2                    | 33                         | 8.25               |
| 2006 | 16                | 9                     | S 4 M 4                    | 35.06                      | 13.88              |
| 2005 | 4                 | 4                     | S 2 M 2                    | 35.25                      | 9.25               |
| 2004 | 7                 | 6                     | S 4 M 2                    | 33.14                      | 9.28               |
| Total| 137               | 107                   | S 65 (61%) M 39 (36%) M 3 (3%) | 29.63±19.51                | 11.28±5.46         |

Abbreviations: m, mild hemophilia A; M, moderate hemophilia A; S, severe hemophilia A.
and major and minor surgical cases in the orthopedic and other surgery group.

**Methods of factor consumption**

In the WFH guidelines presented in 2020, it provides detailed information including the amount of hemostatic agent and duration of treatment depends on the site and severity of bleeding (Table 1) [5]. According to WFH guidelines, recommended maintenance of 80–100% factor VIII activity for the first 1–7 days in severe bleeds and 1–3 days in major operation [5]. We treated hemophilia patients according to WFH guidelines and aimed to maintain 100% factor VIII activity in the first 3 days of admission, both in the cases of severe bleeds and major surgeries. In case of moderate bleeds and minor surgeries, it was flexible, 1–3 days of maintaining normal hemostasis was recommended depending on the clinical situation. Also, the factor concentrate injection was recommended to be progressively reduced depending on the patient’s clinical situation after first 1–3 days. After initial treatment, it was easy to reduce the dose of CFCs if there was no bleeding tendency or if recovery was good after surgery.

**Statistical analysis**

SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. Data was expressed as mean, standard deviations. Parametric analysis was performed using one-way analysis of variance with Student’s t-test. The chi-square test was used to assess the difference between major bleeds and minor bleeds, as well as major operation and minor operation. P-value <0.05 was considered statistically significant.

**Ethics statement**

The Institutional Review Board of Eulji University Hospital approved this study.

### RESULTS

#### Patient characteristics, cause of admission and overall outcomes

Overall, 107 patients with HA were admitted to the Eulji university hospital between January 2004 and December 2018. The number of admission cases was 137 because some

#### Table 3. Bleeds needed for hospitalization and used amount of CFCs.

|                                      | Mean age (yr) | Severity (N of cases) | N of case | Hospitalized days (day) | Amount of CFCs per kg (IU/kg) |
|--------------------------------------|---------------|-----------------------|-----------|-------------------------|-------------------------------|
|                                      |               |                       |           | Total                   |                               |
| Major bleeds                          |               |                       |           | First 3ds               | After 3ds                     |
| CNS bleed                            | 26.3±20.1     | S 5                   | 10        | 36.27±59.4              | 579.5±494.0                  |
|                                       |               | M 5                   |           |                         | 213.7±114.9                  |
|                                       |               |                       |           |                         | 202±176.4                    |
| GI bleed                             | 45.3±12.2     | S 2                   | 17        | 5.6±2.6                 | 975.2±714.1                  |
|                                       |               | M 13                  |           |                         | 191.4±103.5                  |
|                                       |               | m 2                   |           |                         | 77.9±74.3                    |
| Iliopsoas bleed                      | 25.1±13.2     | S 4                   | 7         | 11.3±13.1               | 473.1±300.6                  |
|                                       |               | M 3                   |           |                         | 179.6±160.1                  |
|                                       |               | m 2                   |           |                         | 188.2±129.9                  |
| Compartment syndrome                 | 42.1±1.4      | S 1                   | 2         | 19.0±16.9               | 353.0±79.2                   |
|                                       |               | M 1                   |           |                         | 188.2±129.9                  |
|                                       |               | m 1                   |           |                         | 98.5±25.7                    |
| Ophthalmic hemorrhage\(^a\)          | 32.9±9.1      | S 3                   | 7         | 8.6±4.7                 | 488.1±481.2                  |
|                                       |               | M 4                   |           |                         | 152.0±120.6                  |
|                                       |               |                       |           |                         | 135.3±128.9                  |
| Major bleeds total/average           | 35.1±2.7      | S 15                  | 43        | 15.4±9.98               | 460.3±66.4                   |
|                                       |               | M 26                  |           |                         | 187.2±114.8                  |
|                                       |               | m 2                   |           |                         | 142.7±139.6                  |
| Moderate bleeds                      |               |                       |           | Total                   |                               |
| Dental bleed                         | 22.8±17.7     | S 5                   | 12        | 3.2±1.6                 | 127.2±79.2                   |
|                                       |               | M 7                   |           |                         | 121.3±68.7                   |
| Joint bleed                          | 32.0±21.7     | S 8                   | 14        | 9.1±7.7                 | 359.2±300.8                  |
|                                       |               | M 6                   |           |                         | 262.2±208.9                  |
| Intramuscular bleed\(^b\)            | 28.9±23.4     | S 5                   | 9         | 8.2±6.9                 | 524.7±513.7                  |
| Large ecchymosis                     | 15.4±7.1      | S 5                   | 5         | 5.6±3.05                | 214.2±154.0                  |
| Moderate bleeds total/average        | 26.8±3.1      | S 23                  | 40        | 6.7±6.1                 | 334.4±54.9                   |

\(^a\) Vitreous hemorrhage, Hematoma of eyeball. \(^b\) Intramuscular bleed, excluding: iliopsoas bleed. \(^c\) P-value less than 0.05 is regarded as statistically significant in comparison with Major and moderate bleeds.

Abbreviations: m, mild hemophilia A; M, moderate hemophilia A; S, severe hemophilia A.
patients were admitted more than once. Their mean age on admission was 29.63±19.51 years and mean admission days were 11.25±5.46 days. Most admissions occurred in severe (61%) and moderate (36%) patients. Only 3 cases of admission occurred in patients with mild HA (Table 2). Annually, 9.8 cases of admission were observed during 14 year period, comprising about 8% of the average total registered patients with HA in this HTC. The most common cause of admission was bleed control; 83 cases were admitted to control severe and moderate bleeds (Table 3). The second most common cause of admission was orthopedic surgery and other surgeries of various types (Table 4, 5). Nineteen cases of admission were not related to bleed control and surgery; the most common cause was physiotherapy (Table 6).

| Table 4. Orthopedic surgeries and used amount of CFCs. |
|---------------------------------------------------------|
| Mean age (yr) | Severity | N of case | Hospitalized days (day) | Amount of CFCs per kg (IU/kg) |
|---------------|----------|-----------|-------------------------|------------------------------|
|               |          |           |                         | Total | First 3ds | After 3ds |
| Major operation |          |           |                         |       |           |           |
| ORIF          | 30±8.2   | S 1       | 3                       | 34.7±15.8 | 359.2±110.2 | 123.8±41.2 | 123.6±20.8 |
| Synovectomy   | 20.4±13.3| S 4       | 7                       | 17.4±10.2 | 979.5±519.5 | 267.7±140.8 | 211.1±95.1 |
| Spinal stenosis operation | 68 | S 1 | 1 | 50 | 1,040 | 325 | 150 |
| Open fracture operation | 28.5±12.2 | S 2 | 4 | 20.25±5.4 | 601.6±116.6 | 222.7±138.5 | 140±22.8 |
| Major operation | 27.7±15.9 | S 8 | 15 | 23.8±14.9 | 758.7±733.3 | 209.2±131.7 | 174.1±74.7 |
| Minor operation |          |           |                         |       |           |           |
| Endoscopic synovectomy | 19±17.3 | S 2 | 3 | 4.3±3.2 | 165.7±59.5 | 69.6±24.2 | 78 |
| Closed fracture operation | 7.3±2.3 | S 3 | 3 | 3.3±0.6 | 123.4±53 | 121.3±53.8 | - |
| Minor operation total/average | 13.2±12.8 | S 5 | 6 | 5.8±4.9 | 143.5±56.2 | 95.5±46.9 | 78 |

\[ P^a 0.48 \]

\[ P^b 0.018 \]

\[ P^c 0.040 \]

\[ P^d 0.020 \]

\[ P^e 0.527 \]

\[ P^f 0.09 \]

\[ P^g 0.04 \]

\[ P^h 0.000 \]

\[ P^i 0.005 \]

\[ P^j 0.198 \]

\[ P^k 0.09 \]

\[ P^l 0.04 \]

\[ P^m 0.000 \]

\[ P^n 0.005 \]

\[ P^o 0.198 \]

\[ P^p 0.09 \]

\[ P^q 0.04 \]

\[ P^r 0.000 \]

\[ P^s 0.005 \]

\[ P^t 0.198 \]

\[ P^u 0.09 \]

\[ P^v 0.04 \]

\[ P^w 0.000 \]

\[ P^x 0.005 \]

\[ P^y 0.198 \]

a) P-value less than 0.05 is regarded as statistically significant in comparison with major and minor operation. Abbreviations: M, moderate hemophilia A; ORIF, open reduction and internal fixation; S, severe hemophilia A.

| Table 5. Other surgeries and used amount of CFCs. |
|---------------------------------------------------------|
| Mean age (yr) | Severity | N of case | Hospitalized days (day) | Amount of CFCs per kg (IU/kg) |
|---------------|----------|-----------|-------------------------|------------------------------|
|               |          |           |                         | Total | First 3ds | After 3ds |
| Major operation |          |           |                         |       |           |           |
| Appendectomy  | 16       | S 1       | 1                       | 4     | 314.3 | 208.3 | 124 |
| Splenectomy   | 23       | S 1       | 1                       | 31    | 231.9 | 139.1 | 139 |
| Craniotomy & closed drainage | 38.75±12.1 | S 4 | 4 | 67.5±53.9 | 1069.9±507.4 | 337±87.1 | 371.5±153.0 |
| Adenoidectomy | 3        | S 1       | 1                       | 6     | 712.5 | 437.5 | 393 |
| Tooth extraction (> 3) | 47.7±12.2 | M 3 | 3 | 3.7±0.6 | 178.1±48.7 | 178.1±48.7 | - |
| Major operation total/average | 34.5±16.7 | S 7 | 10 | 32.2±24.3 | 578.9±487.1 | 217.3±143.3 | 271.4±166.8 |
| Minor operation |          |           |                         |       |           |           |
| Hemorrhoidectomy | 25.6±4.6 | S 3 | 3 | 4     | 288.3±89.0 | 196.9±8.9 | 78 |
| Removal of lipoma | 39       | M 1       | 1                       | 6     | 120   | 60    | 60 |
| Tooth extraction (≤2) | 23.0±14.7 | S 1 | 3 | 1.3±0.6 | 68.6±33.4 | 68.6±33.4 | - |
| Tympanoplasty   | 44       | S 1       | 1                       | 13    | 73.8  | 73.8  | -   |
| Colonoscopic resection or Bx | 25.7±7.6 | M 3 | 3 | 3.3±2.2 | 182.1±38.6 | 182.1±38.6 | - |
| Minor operation total/average | 31.6±11.5 | S 5 | 11 | 4.5±3.5 | 179.0±112.8 | 137.6±66.8 | 98.0±28.3 |

\[ P^a 0.09 \]

\[ P^b 0.04 \]

\[ P^c 0.000 \]

\[ P^d 0.005 \]
Table 6. Cause of admissions unrelated to acute bleeds and surgeries.

|                      | Mean age (yr) | Severity (N of cases) | N of cases | Hospitalized days | Amount of CFCs per kg (IU/kg) |
|----------------------|---------------|-----------------------|------------|------------------|-------------------------------|
| DM                   | 36            | Severe 1              | 1          | 6                | 266.1                         |
| Pneumonia            | 6.0±7.0       | Severe 2              | 2          | 5.5±2.1          | 100.0±70.7                    |
| Pancreatitis         | 42            | Mild 1                | 1          | 15               | 140.2                         |
| Liver cirrhosis      | 41.3±0.6      | Mild 3                | 3          | 7.6±6.4          | 98.0±68.3                     |
| Colitis              | 20            | Severe 1              | 1          | 5                | 44.1                          |
| APN                  | 22.5±12.0     | Severe 2              | 2          | 4±1.4            | 70.9±41.1                     |
| Chemotherapy         | 69            | Severe 1              | 1          | 38               | 465                           |
| Dialysis             | 70            | Severe 2              | 2          | 17.5             | 326.6±85.5                    |
| PT                   | 30.7±22.9     | Severe 5              | 5          | 21.5±17.8        | 338.4±197.9                   |
| OBS                  | 7.6±7.8       | Severe 5              | 5          | 6.6±5.5          | 667.7±609.4                   |
| Total/average        | 29.0±23.4     | Severe 19             | 23         | 12.5±11.4        | 324.0±317.3                   |

Abbreviations: APN, acute pyelonephritis; OBS, hospitalized for observation; PT, physical therapy.

Table 7. Comparison of all major operations and minor operations.

|                      | Mean age (yr) | Severity (N of cases) | N of case | Hospitalized (day) | Amount of CFCs per kg (IU/kg) | Amount of CFCs first 3 days | Amount of CFCs After 3 days |
|----------------------|---------------|-----------------------|-----------|--------------------|-------------------------------|-----------------------------|-----------------------------|
| Major operation      | 25.5±15.9     | S 15                  | 25        | 23.7±3.9           | 541.7±432.2                   | 209.5±134.0                 | 173.5±92.3                  |
| Minor operation      | 21.0±13.8     | S 9                   | 16        | 8.0±7.4            | 276.8±188.9                   | 117.9±61.8                  | 91.3±23.1                   |
| Pa)                  | 0.683         | 0.028                 | 0.018     | 0.090              | 0.072                         |                             |                             |

Pa) P-value less than 0.05 is regarded as statistically significant in comparison with major and minor operation.

Results of the patients admitted for bleed control

The number of admission cases to control severe and moderate bleeding was not different. The mean age of the patients admitted to control severe bleeding events was 35.1±2.7 years. The most commonly observed severe bleeds were GI hemorrhages. Most cases of severe bleeds were observed in severe (37.2%) and moderate (60.5%) hemophilia patients; however, 2 cases of GI hemorrhage were observed in mild hemophilia patients. The mean admission days were 15.4±9.98 and the quantity of CFCs used was 460.5±66.4 IU/kg. The largest quantity of CFCs per body weight was used to control GI bleeds (975.2±714.1 IU/kg) followed by the amount used to control hemorrhage (359.2±300.8 IU/kg). All the moderate bleeds were successfully controlled without any sequelae. No inhibitors for FVIII were observed in these patients. Although severe bleed tends to occur in older age, there were no significant differences in admission age between cases of severe and moderate bleeds. However, the admission days (P=0.021) and total consumption of CFC (P=0.042) were significantly different between cases with severe bleeds and moderate bleeds.

Results of the patients admitted for orthopedic surgery

Major orthopedic operations were performed in 15 cases, and the mean age of patients was 27.7±15.9 years (7–39). The type of major orthopedic surgery included open reduction and internal fixation, synovectomy, spinal stenosis operation, and open fracture operation. The mean length of hospital stay was 23.8±14.9 days and the amount of CFCs used was 758.7±733.3 IU/kg. Overall, 6 minor orthopedic surgeries, 3 endoscopic synovectomies, and 3 closed fracture surgeries were performed in 6 patients with severe and moderate HA. The mean length of hospital stay was 5.8±4.9 days, and the amount of CFCs used was 143.5±56.2 IU/kg.
There was significant difference in the amount of CFCs used ($P=0.04$) and in the mean hospital stay ($P=0.018$) between major and minor orthopedic surgical cases. All the surgeries were performed without any significant complications.

**Results of the patients admitted for Non-orthopedic surgeries**

Non-orthopedic surgeries were categorized as major and minor surgery. Ten cases of major operations were performed in 7 patients with severe HA and 3 patients with moderate HA. The mean hospital stay was 32.2±24.3 days, the mean age was 34.5±16.7 (3-48) years, and the amount of factor VIII CFC used was 578.9±487.1 IU/kg. Eleven cases of minor operations were performed for 5 patients with severe HA and 6 patients with moderate HA. The mean hospital stay was 4.5±3.5 days, and the total amount of factor VIII CFC used was 179.0±112.8 IU/kg. Longer admission days were observed in major operation and more FVIII CFC was consumed in major operation ($P<0.001$). All the surgeries were performed without any complications and no cases of death were observed except a case of death caused by sepsis, not by hemorrhage that occurred in a patient after brain surgery.

**Results of the patients admitted for reasons other than control of bleeds and surgery**

Twenty-three patients, 19 with severe HA and 4 with mild HA, were admitted for various reasons other than bleed control and surgeries. The mean age at admission was 29.0±23.4 years (6-70). The most common cause of admission was for physical therapy in 5 patients with severe HA. The mean admission days was 12.5±11.4 and FVIII CFC 324.0±317.3 IU/kg was consumed for the prevention of bleeds in cases of invasive procedures and bleeds occurred during the admission period. Only one case of death was observed, which was caused by sepsis that occurred in a patient with end-stage renal failure.

**Results of CFC consumption in the first 3 days and after 3 days of admission of patients in bleeding and surgery group**

The CFC consumptions in the first 3 days of admission were 187.2±114.8 IU/kg (40.65% of the total dose), 209.2±131.7 IU/kg (29.37%), and 217.3±143.3 IU/kg (37.54%) for the cases of severe bleeds, major orthopedic surgery, and major non-orthopedic surgery, respectively. The CFC consumptions in the first 3 days of admission were 183.3±145.0 IU/kg (54.81%), 95.5±46.9 IU/kg (66.55%), and 137.6±66.8 IU/kg (76.87%) for the cases of moderate bleeds, minor orthopedic surgery, and minor non-orthopedic surgery, respectively. The CFC consumptions after 3 days of admission were 68.5±60.7 IU/kg (20.48%), 78 IU/kg (47.07%), and 98.0±28.3 IU/kg (54.75%) for the cases of moderate bleeds, minor orthopedic surgery, and minor non-orthopedic surgery, respectively.

In all the surgeries combined, the mean total amount of CFC used was 541.7±432.2 IU/kg in major surgeries during 23.7±3.9 admission days, 209.5±134.0 IU/kg (38.67%) for the first 3 days, and 173.5±92.3 IU/kg (32.02%) after 3 days. In minor operations, the total amount of CFC used was 276.8±188.9 IU/kg during the 8.0±7.4 admission days, 117.9±61.8 IU/kg (42.59%) for the first 3 days, and 91.3±23.1 IU/kg (32.98%) after 3 days (Table 7).

**DISCUSSION**

Hemophilia treatment is costly due to the high cost of CFCs; therefore, a cost-effective guideline is required for hemophilia treatment, especially for CFC supplementation on admission. Several guidelines of HTCs and WFH (The World Federation of Hemophilia) are currently used for this purpose but there are weak scientific evidences of the optimal level of hemostasis and maintenance duration in these guidelines. This is because the actual dose and maintenance duration required for bleeding control and successful surgery are determined empirically due to the wide range of required hemostatic levels and maintenance duration in these patients [5, 9-11]. With respect to the optimal level of factor activity, the needed level for hemostasis has a wide range: FVIII:C 5-40% for mild and moderate bleeding and FVIII:C 50-150% for severe bleeding or trauma and surgery. Additionally, there is weak evidence of maintenance duration of this level to ensure hemostasis or prevent re-bleedings, especially severe bleedings [5, 9-17]. Furthermore, in surgical cases, there is no reliable scientific evidence of optimal hemostatic levels and maintenance duration for wound healing in hemophilia patients [9, 10, 13-19]. Therefore, the WFH guideline, which is most frequently used guideline; suggests different guidelines for dosing of CFCs depending on the availability of CFCs in each country [5, 9-19].

Despite these ambiguities, rapid and early hemostasis and maintenance of normal stable hemostasis should be provided during the early phase of severe bleeding, during the surgical procedures, and early post-operative period. Thus, most guidelines, including the WFH guideline, recommend maintenance of normal hemostasis at least for initial 1–3 days, despite of the wide ranges of normal hemostatic levels (50–150% FVIII:C) and maintenance duration (1–7 days) [5, 9-18]. Therefore, in the first 3 days of admission, we aimed to maintain 100% FVIII activity, both in the cases of severe bleedings and major surgeries, whereas the WFH guideline recommends to maintain 80–100% FVIII activity for the first 1–7 days in severe bleeding and 1–3 days in major operation. In cases of moderate bleedings and minor surgeries, it was flexible; 1–3 days of maintaining normal hemostasis was recommended depending on the clinical situation. After that period, WFH and other HTC guidelines recommend to continue CFC infusion to maintain optimal hemostasis for wound healing in surgery and to ensure stable hemostasis for preventing re-bleedings in bleeding control.
However, there are weak scientific evidences of the optimal FVIII activity level and maintenance duration after the first days of treatment as previously mentioned. Therefore, we did not strictly follow the WFH guideline. After acquiring initial stable hemostasis for 1–3 days, it was recommended to progressively reduce the dose depending on the context of individual cases in all the admitted patients for bleed control or surgery.

This strategy had been used since the early 2000s for admitted HA patients. The present study reported the results of admission cases and mainly focused on CFC consumption and outcomes of the admission since then for 14 years.

This observation study showed that the average total CFC dose consumed for severe bleeding and all the major surgeries was lower than the consumed dose in other reports [20–24] and the average required CFC dose is supposed to be followed by WFH dosing recommendation for countries without CFC restriction [5, 9–14].

The average dose consumed in the first 3 days was 204.4 IU/kg for patients admitted for the control of severe bleeds and major surgeries in this study. The consumed dose was nearly equal to the required dose to maintain 3 day FVIII activity of 100%. This suggests that in most of these cases, nearly 100% of FVIII activities might be maintained for 3 days for successful control of severe bleeds and major surgeries, considering the mean age (32.4 yr) of these patients. In this age group, the average HL of FVIII is around 12 h (Based on Korean FVIII PK data, not published).

Thus, lower total dose consumption in cases of severe bleedings and major surgeries was mainly due to the effect of less dose consumption after the first 3 days of admission, because the dose administered to the patients for the initial 3 days is not different from the dosing recommendation of WFH. Conversely, we did not follow the WFH guideline of FVIII CFC dosing after acquiring initial stable hemostasis for 3 days and treated the patients depending on the context of individual cases as mentioned. This modulation might result in less CFC consumption after initial stable hemostasis for 3 days. Despite this lower dose consumption after 3 days, all the severe bleeds were well controlled and all the major surgeries were successfully conducted.

With respect to the total CFC consumption in admitted cases of moderate bleeds and minor surgeries, the comparison was difficult because of rarity of reports for these cases; however, the total consumption in minor surgeries was lower than the required average dose consumption following WFH recommendations for minor surgeries.

In contrast to the admission cases of severe bleeding and major surgeries, 100% FVIII activity was maintained for only 1 day in most cases of minor surgeries in this study. The average CFC consumption in the first 3 days was 138.8 IU/kg in these patients, which was the needed dose to maintain 100% FVIII activity for only for 1 day and a maximum of 2 days when the HL of FVIII in a patient was long enough. However, this maintenance of 100% FVIII activity for the first day of admission was higher than the level recommended in WFH (50–80% for a day), thus lower total dose consumption in minor surgeries may be due to lesser dose consumption after the initial days. Despite this lower dose consumption, all the minor surgeries were successfully conducted.

The relatively higher dose consumption in controlling moderate bleeds in this study may be due to refractory bleeds, which are the causes of admission in most patients. To overcome the refractoriness, nearly double the dose for control of moderate bleeds were administered to the patients for the first 1–3 days of admission; therefore, the CFC consumption in the first 3 days was not different compared to that for the admission cases for controlling severe bleeds. The cause of refractoriness was unknown in most cases; however, no cases of newly developed inhibitors to FVIII were detected.

CONCLUSION

In conclusion, all the bleeds were successfully controlled and all surgeries were also successfully performed with this dosing strategy for admitted HA patients in a Korean HTC. This result suggest that it is necessary to develop more specified regimens different from WFH guidelines of CFC supplementation for admitted Korean HA patients, especially after initial stable hemostasis is achieved.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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