The efficacy of bypassing agents in surgery of hemophilia patients with inhibitors

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Background
Inhibitory antibodies to factor VIII (FVIII) or IX (FIX) are important issues when managing patients with hemophilia A or B. Advances in bypassing agents such as recombinant activated FVII (rFVIIa) and activated prothrombin complex concentrates (APCC) have enabled the aggressive management of hemophilia with inhibitors during emergency or elective surgery. This study provides an updated evaluation of the safety and effectiveness of bypassing agents in treating perioperative bleeding.

Methods
We reviewed the records of hemophilia patients with inhibitors who underwent surgery between May 2008 and July 2014 using bypassing agents or high-dose FVIII concentrates at a single center.

Results
In total, 36 surgeries (24 orthopedic, 12 other) were conducted in 18 hemophilia patients with inhibitors. The median inhibitor titer at surgery was 14 (range, 0.7–1,900) Bethesda units. Most patients had high-responding inhibitors. In total, 25 patients received APCC, 9 with rFVIIa initially. In most cases, bleeding stopped or was well controlled; however, bleeding in 6 patients was controlled using sequential bypassing therapy. Hemostatic efficacy of bypassing agents in various surgeries, based on the final patient outcome, was 94.4% (34/36). Among 5 emergency surgeries, 2 deaths occurred.

Conclusion
Good control of hemostasis can be achieved using bypassing agents in hemophilia patients with inhibitors who are undergoing surgery. Thorough planning is needed before elective surgery and more active and aggressive management may be needed for emergency surgery. Use of bypassing agents can facilitate safe and successful surgeries in hemophilia patients with inhibitors.

Key Words
Hemophilia, Inhibitor, Bypassing agent, Surgery
and prevent bleeding during the perioperative period in hemophilia patients with inhibitors [1, 2, 6-8]. Two types of bypassing agents are currently available in the clinical setting: activated prothrombin complex concentrates (APCC) (FEIBA, Baxter, Vienna, Austria) and recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark). A few clinical studies have shown that bypassing agents can be safe, effective treatments to manage bleeding before and after surgery and to prevent bleeding in hemophilia patients with inhibitors [1, 2, 6, 7]. However, the number of reported cases involving emergency conditions and elective surgeries remains limited, and a consensus regarding the efficacy and safety of bypassing agents is still needed.

Given this background, we conducted this single-center, retrospective study to assess the hemostatic efficacy and safety of bypassing agents in hemophilia patients with inhibitors undergoing elective or emergency surgeries. The aim of this study was to identify the possibility of surgical intervention in hemophilia patients with inhibitors by using bypassing agents while under the care of hematologists.

MATERIALS AND METHODS

Study patients and setting

Between May 2008 and July 2014, 18 patients underwent 36 surgeries at our medical institution. Hemophilia patients with inhibitors who underwent surgery and were hospitalized for hemostatic therapy were included. Inhibitors were classified into low- or high-responding inhibitors based on a patient’s peak inhibitor titer after repeated FVIII exposure. An antibody titer persistently below 5 Bethesda units (BU) despite repeated challenges with FVIII was considered a low-responding inhibitor. A high-responding inhibitor was defined as a titer greater than 5 BU at any time [9]. This study was approved by the Institutional Review Board of our medical institution (approval No. 2015-01-028).

Treatment protocol

High-dose FVIII concentrates (100 IU/kg twice daily) were used in the low-responding inhibitor group. In the high-responding inhibitor group, bypassing agents were administered following the manufacturer’s guidelines for optimal dosing: 50-100 U/kg for APCC and 90-120 μg/kg for rFVIIa [10, 11]. APCC was administered every 8-12 hours but did not exceed 200 IU/kg/day for the first 3 days [12]. The rFVIIa was administered every 2-3 hours in doses of 90 μg/kg for the first 3 days. The infusion regimens of bypassing agents were prescribed in accordance with a nationally approved summary of product characteristics or in accordance with guidance from current published literature [6, 13]. The treatment dose was tapered depending on the type of surgery and clinical outcomes. If surgery was performed under general anesthesia or if the surgery was orthopedic, we reduced the dose or frequency of clotting factor concentrates after using the current product for the first 3 days. If the procedure was performed under local anesthesia, we controlled the use of hemostatic coverage after the first 2 days. Considering clinical outcomes, if the bleeding worsened or the patient did not improve, additional changes in treatment were made such as switching products or increasing the dose or frequency of the current product. Because the maximum dose of bypassing agent was administered at the beginning of the surgery, the agent was changed if there was unsatisfactory bleeding control.

If patients with hemophilia and inhibitors experienced bleeding episodes that were refractory to either APCC or rFVIIa alone, both products were administered in a sequential fashion to produce a superior hemostatic outcome. Sequential therapy was defined as the alternate administration of 1 APCC dose followed by 1 or 2 rFVIIa doses within 12 hours.

Patient evaluation

Through a retrospective review of the medical records, we evaluated preoperative baseline characteristics such as age, gender, weight, type and severity of hemophilia, inhibitor titers, medical history, type of surgery, type of initial bypassing agent, initial treatment regimens, and outcomes of prophylactic treatment. We also evaluated patient outcomes based on perioperative bleeding, time to change of initial clotting factor concentrate, use of sequential therapy, total amount of clotting factor concentrates, reoperation or additional surgery, length of hospital stay, and patient outcomes such as the rate of patient discharge.

Patient follow-up

Postoperatively, the patients were followed up once during the first 1-month period, at 6-month intervals for the following year, and once per year during the second and third years.

Table 1. Patient demographics.

| Value |
|-------|
| Number of patients, N (gender) | 18 (all male) |
| Number of procedures evaluated, N | 36 |
| Orthopedic | 25 |
| Other | 11 |
| Median age, years (range) | 30.5 (7-52) |
| Type of hemophilia, N (%) | |
| Hemophilia A | 16 (88.9%) |
| Hemophilia B | 2 (11.1%) |
| Severe hemophiliaa, N | 18 |
| Type of inhibitors, N | |
| Low-responding | 2 |
| High-responding | 34 |
| Inhibitors titer at procedures | |
| Median, BU (range) | 14 (0.7-1,900) |
| < 5 BU, N (%) | 15 (41.7%) |
| ≥ 5 BU, N (%) | 21 (58.3%) |

aSevere hemophilia was defined as <1% clotting factor level. Abbreviation: BU, Bethesda unit.
## RESULTS

### Baseline characteristics of the patients

In total, 36 surgeries were conducted in 18 hemophilia patients with inhibitors (Table 1). The median age of the patients was 30.5 (range, 7–52) years. Our clinical series of patients comprised 16 cases of hemophilia A (88.9%) and 2 cases of hemophilia B (11.1%). All of the patients had severe hemophilia, which shows less than 1% of normal factor activity in blood. The median inhibitor titer at procedures was 14 (range, 0.7–1,900) BU. Of the 36 surgeries, 25 were elective orthopedic surgeries, and the remaining 11 comprised a variety of surgical procedures, 5 of which occurred under emergency conditions. All surgeries were performed using standard conventional methods at a single center, for which the patients' hematologic profile was monitored by a single board-certified specialist in hematology. Moreover, each procedure is reported as an individual case (Tables 2 and 3).

### Patient progress

Patient progress and outcomes are described in Table 4. The median length of hospital stay was 14 (range, 1–58) days. High-dose FVIII concentrates were given in 2, APCC in 21, and rFVIIa in 9 cases (Table 1). In 10 cases, however, we replaced the initial hemostatic cover with other medi-

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### Table 2. Details of the cases and procedures.

| Case No. | Initial hemostatic cover | Change of Tx | Sequential therapy | Bypassing agents | Dosage (IU/kg) | Transfused RBCs (U) | ICU care |
|----------|--------------------------|--------------|---------------------|------------------|----------------|---------------------|---------|
|          |                          |              |                     | Total administration duration (d) | FVIII  | APCC  | rFVIIa | FVIII  | APCC  | rFVIIa |                |
| A1       | APCC                     | No           | No                  | NA               | 17   | NA    | 17     | NA     | 2,094 | NA     | 0               | No       |
| B1       | APCC                     | No           | No                  | NA               | 1    | NA    | 113    | NA     | 1,097 | NA     | 0               | No       |
| B2       | APCC                     | No           | No                  | NA               | 10   | NA    | 1,130  | NA     | 10    | NA     | 0               | No       |
| B3       | rFVIIa                   | No           | No                  | NA               | 6    | NA    | 130    | NA     | 0     | NA     | 0               | No       |
| C1       | FVIII                    | →APCC        | No                  | 3                | 13   | 8     | 335    | 1,520  | 125   | 0     | No               |
| C2       | FVIII                    | →rFVIIa      | No                  | 8                | 12   | 960   | 226    | 4      | 0     | No               |
| D1       | APCC                     | No           | No                  | NA               | 10   | NA    | 1,651  | NA     | 0     | NA     | 0               | No       |
| D2       | APCC                     | →rFVIIa      | Yes                 | NA               | 52   | 3     | 5,916  | 30     | 26    | Yes              |
| D3       | APCC                     | No           | No                  | NA               | 3    | NA    | 411    | NA     | 6     | Yes              |
| E1       | APCC                     | →rFVIIa      | No                  | NA               | 16   | 1     | 1,209  | 13     | 0     | No               |
| E2       | APCC                     | No           | No                  | NA               | 6    | NA    | 455    | NA     | 0     | No               |
| E3       | APCC                     | →rFVIIa      | No                  | NA               | 11   | 3     | 1,464  | 31     | 2     | No               |
| F1       | APCC                     | No           | No                  | NA               | 5    | NA    | 594    | NA     | 0     | No               |
| F2       | APCC                     | No           | No                  | NA               | 7    | NA    | 958    | NA     | 0     | No               |
| F3       | APCC                     | No           | No                  | NA               | 8    | NA    | 1,402  | NA     | 0     | No               |
| G1       | APCC                     | No           | No                  | NA               | 10   | NA    | 1,277  | NA     | 0     | No               |
| H1       | rFVIIa                   | No           | No                  | NA               | 11   | NA    | 194    | NA     | 0     | No               |
| H2       | rFVIIa                   | No           | No                  | NA               | 9    | NA    | 137    | NA     | 0     | No               |
| I1       | rFVIIa                   | No           | No                  | NA               | 21   | NA    | 517    | 3      | 0     | No               |
| J1       | APCC                     | No           | No                  | NA               | 8    | NA    | 1,145  | NA     | 0     | No               |
| K1       | rFVIIa                   | No           | No                  | NA               | 11   | NA    | 303    | 9      | 0     | No               |
| K2       | rFVIIa                   | No           | No                  | NA               | 21   | NA    | 457    | 2      | 0     | No               |
| K3       | rFVIIa                   | No           | No                  | NA               | 25   | NA    | 414    | 0      | 0     | No               |
| L1       | rFVIIa                   | →APCC        | Yes                 | NA               | 15   | 26    | 1,651  | 600    | 8     | No               |
| L2       | rFVIIa                   | →Seq.        | Yes                 | NA               | 6    | 17    | 687    | 365    | 5     | No               |
| M1       | APCC                     | →Seq.        | Yes                 | NA               | 16   | 3     | 2,565  | 27     | 8     | Yes              |
| N1       | APCC                     | No           | No                  | NA               | 12   | NA    | 1,752  | NA     | 0     | No               |
| N2       | APCC                     | No           | No                  | NA               | 18   | NA    | 2,514  | NA     | 0     | No               |
| N3       | APCC                     | No           | No                  | NA               | 18   | NA    | 2,514  | NA     | 0     | No               |
| N4       | APCC                     | No           | No                  | NA               | 14   | NA    | 4,269  | NA     | 0     | No               |
| O1       | APCC                     | →Seq.        | Yes                 | NA               | 2    | 1     | 200    | 19     | 10    | No               |
| P1       | rFVIIa                   | No           | No                  | NA               | 13   | NA    | 329    | 0      | Yes              |
| Q1       | APCC                     | No           | No                  | NA               | 2    | NA    | 169    | NA     | 0     | No               |
| Q2       | APCC                     | No           | No                  | NA               | 11   | NA    | 1,330  | NA     | 0     | No               |
| R1       | APCC                     | No           | No                  | NA               | 17   | NA    | 1,866  | NA     | 0     | No               |
| R2       | APCC                     | →rFVIIa      | Yes                 | NA               | 31   | 7     | 3,748  | 11     | 38    | Yes              |

Abbreviations: FVIII, factor VIII concentrate; APCC, activated prothrombin complex concentrates; rFVIIa, recombinant activated factor VII; NA, not applicable; Seq, sequential.

*Procedures for N2 and N3 were done on the same day.*
Table 3. Surgeries performed.

| Type of surgery                                      | Case No. | N  |
|------------------------------------------------------|----------|----|
| Orthopedic                                           |          |    |
| Total knee replacement                               | C1, C2, D1, E3, H1, K2, K3, L1, L2 | 9  |
| Total hip replacement                                | K1       | 1  |
| Arthroscopic synovectomy                             | F1, F2, F3, G1, H1, J1, JN1, N2, Q2 | 9  |
| Amputation of the leg                                | A1       | 1  |
| Closed reduction of ankle dislocation                | E1       | 1  |
| Device removal from the leg                          | E2       | 1  |
| Finger tenotomy                                      | B2       | 1  |
| Hematoma evacuation of hand                          | R1       | 1  |
| Open reduction of femur fracture with internal fixation | H2       | 1  |
| Other                                                |          |    |
| ICH removal and craniectomy (emergency)              | D3       | 1  |
| Polypectomy of the colon                             | N4       | 1  |
| Exploratory thoracotomy (emergency)                  | M1       | 1  |
| Myringotomy with insertion of tube                   | B1       | 1  |
| Segmental resection of the small bowel (emergency)   | D2, R2   | 2  |
| Circumcision                                         | D3, N3   | 2  |
| Catheter insertion (chemoport, PICC)                 | B3, O1   | 2  |
| Arterial embolization (emergency)                    | D1       | 1  |

Abbreviations: ICH, intracranial hemorrhage; PICC, peripherally inserted central catheter.

Table 4. Patient progress and outcomes.

| Value                                                                 |
|-----------------------------------------------------------------------|
| Median duration of hospitalization, days (range)                      |
| 14 (1–58)                                                             |
| Initial hemostatic cover, N                                           |
| FVIII concentrates                                                    |
| 2                                                                    |
| APCC                                                                  |
| 25                                                                   |
| rFVIIa                                                                |
| 9                                                                    |
| Changes of initial clotting factor concentrates, N (%)                 |
| 10 (27.8%)                                                           |
| Orthopedic surgery                                                   |
| 6 (24%)                                                              |
| Other surgery                                                        |
| 1 (16.7%)                                                            |
| Emergency surgery                                                     |
| 3 (60%)                                                              |
| Sequential bypassing therapy, N (%)                                   |
| 6 (16.7%)                                                            |
| Orthopedic surgery                                                   |
| 2 (8%)                                                               |
| Other surgery                                                        |
| 1 (16.7%)                                                            |
| Emergency surgery                                                     |
| 3 (60%)                                                              |
| Patient outcome, N (%)                                                |
| Discharge                                                             |
| 34 (94.4%)                                                           |
| Death                                                                |
| 2 (5.6%)                                                             |

Abbreviations: FVIII, factor VIII; APCC, activated prothrombin complex concentrates; rFVIIa, recombinant activated factor VII.

Postoperative bleeding control in emergency surgery cases

The 36 surgeries included 5 emergency and 31 elective surgeries (Table 5). Two patients (D3 and P1) (2/5, 40%) died after emergency surgeries. Of the remaining 3 patients (D2, M1, and R2), 2 (D2 and R2) had small bowel ischemia and the other (M1) underwent an emergency thoracotomy for hemothorax with hemostatic covering using bypassing agents. In the last 3 cases (D2, M1, and R2), postoperative bleeding control was successful after sequential therapy.

DISCUSSION

Neutralizing antibodies to FVIII or FIX pose problems in the management of patients with hemophilia A or B. It has been reported that both APCC and rFVIIa are effective for bleeding control in hemophilia patients with inhibitors. The hemostatic efficacy of bypassing agents has been docu-
Table 5. Patients who underwent surgery under emergency conditions.

| Case No. | Age (y) | Diagnosis    | Operation                              | Sequential therapy | Result   |
|----------|---------|--------------|----------------------------------------|--------------------|----------|
| D3       | 42      | ICH          | ICH removal and craniectomy            | No                 | Death    |
| P1       | 43      | Hemothorax   | Angiography and arterial embolization  | No                 | Death    |
| D2       | 41      | Small bowel ischemia | Segmental resection of the small bowel | Yes              | Discharge|
| R2       | 44      | Small bowel ischemia | Segmental resection of the small bowel | Yes              | Discharge|
| M1       | 15      | Hemothorax   | Exploratory thoracotomy                | Yes               | Discharge|

Abbreviation: ICH, intracranial hemorrhage.
ing hemostatic and rehabilitative care. Therefore, our ability
to evaluate a patient’s condition after discharge was limited.

In conclusion, our results indicate that postoperative out-
comes can be successful in hemophilia patients with in-
hibitors if bleeding is managed effectively using bypassing
agents during the perioperative period. In addition, our re-
sults indicate that more active and aggressive management
should be performed for patients undergoing emergency
surgery. It is thus imperative that outcome measures for
successful postoperative outcomes based on the hemostatic
efficacy of bypassing agents are customized for individual
hemophilia patients.

Authors’ Disclosures of Potential Conflicts of Interest

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

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