



# Sequential therapy with activated prothrombin complex concentrates and recombinant activated factor VII to treat unresponsive bleeding in patients with hemophilia and inhibitors: a single center experience

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p-ISSN 2287-979X / e-ISSN 2288-0011  
<http://dx.doi.org/10.5045/br.2013.48.4.282>  
**Blood Res 2013;48:282-6.**

Received on September 12, 2013  
Revised on October 18, 2013  
Accepted on November 14, 2013

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## Background

Currently, the greatest challenge in hemophilia treatment is managing hemophilia patients with inhibitors. The two main bypassing agents that are used to treat hemophilia patients with inhibitors are activated prothrombin complex concentrates (APCC) and recombinant factor VIIa (rFVIIa). Hemophilia patients with inhibitors can develop bleeding episodes, that are refractory to monotherapy with either APCC or rFVIIa and thus are often difficult to manage.

## Methods

This report describes a retrospective chart review of four hospitalized patients with severe hemophilia and inhibitors who were treated with sequential therapy of APCC and rFVIIa for refractory bleeding. Sequential therapy was defined as the administration of both rFVIIa and APCC within 12 h.

## Results

In 5 episodes experienced by 4 patients with inhibitors, bleeding was not controlled by single bypass treatment, but it was controlled when two agents were sequentially administered. Sequential therapy was administered by alternating one APCC dose to 1 to 2 rFVIIa doses, with dosing intervals ranging from 3 to 6 h. All bleeding episodes were controlled within 12 to 24 h. Sequential therapy was discontinued after 2 to 5 days. No adverse clinical events, such as thrombosis, were observed.

## Conclusion

Sequential therapy with APCC and rFVIIa was efficacious without adverse events; however, attention on thrombosis is needed. In addition, a prospective clinical trial is needed to provide further evidence for this treatment.

**Key Words** Hemophilia, Inhibitor

## INTRODUCTION

Hemophilia is a severe bleeding disorder, which can result in significant morbidity and mortality [1]. Bleeding episodes are effectively treated by replacing the deficient factor; however, it is common for patients to develop inhibitors to factor VIII or IX, which leads to severe and expensive complications from treatment [2, 3]. The presence of high titer inhibitors, in particular, renders replacement therapy completely ineffective. In such cases, bypassing agents are required to

treat bleeding episodes. Currently, two bypassing agents are available for treating hemophilia patients with inhibitors: activated prothrombin complex concentrates [APCC (FEIBA™, Baxter, Vienna, Austria)] and recombinant activated factor VII [rFVIIa (NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark)]. Both bypassing agents are safe, effective treatments for bleeding episodes in hemophilia patients with inhibitors [4, 5].

Studies have indicated that 10–20% of bleeding events in hemophilia patients with high-responding inhibitors cannot be controlled with a single bypassing agent [6, 7].

Schneiderman and colleagues reported the use of sequential combination of bypassing agents in cases of refractory bleedings [8, 9]. However, treatment with a combination of these agents is not widely practiced due to concerns about developing thromboembolic complications. In this study, we investigated the efficacy and safety of APCC and rFVIIa sequential therapy on management of bleeding that was not controlled by a single bypassing agent.

## MATERIALS AND METHODS

We retrospectively reviewed 5 sequential therapies given to 4 patients with severe hemophilia and inhibitors, all of whom had refractory bleeding with a single bypassing agent. Refractory bleeding was defined as bleeding that was unresponsive to initial therapy with a single bypassing agent and thus required the addition of a second bypassing agent within a reasonable amount of time (12 to 24 h in our study). The sequential infusion of APCC and rFVIIa was used to treat refractory bleeding. Sequential therapy was defined as alternate administration of one APCC dose to 1 to 2 rFVIIa doses within 12 h. APCC was administered every 8 to 12 h as a single bypassing agent in doses of 50–100 IU/kg, with a maximum dose of 200 IU/kg/day. The rFVIIa was administered every 2 to 3 h in doses of 90 µg/kg; the dosing interval was adjusted according to the patient's response.

We collected data regarding demographic characteristics, previous prophylaxis, site of unresponsive bleeding, initial treatment regimen and response, sequential therapy regimen, and any side effects. We also investigated laboratory data, such as complete blood count (CBC), prothrombin time (PT),

activated partial thromboplastin time (aPTT), factor VIII (FVIII) or factor IX (FIX) level, and antibody levels against FVIII or FIX.

## RESULTS

Five courses of sequential bypassing therapies were administered to 4 patients. The median age was 15 years (range, 8–41 years). The clinical characteristics of the patients are displayed in Table 1. All patients were hospitalized for uncontrolled bleeding before sequential therapy. The 5 cases of unresponsive bleeding described below are summarized in Table 2.

The Case 1 patient had a history of peak inhibitor titer that increased to 1,126 Bethesda units (BU). Insertion of a peripheral inserted central catheter (PICC) was planned for immune tolerance induction therapy. APCC was administered before and after the PICC insertion, but bleeding was not controlled. Although treatment was changed from APCC to rFVIIa therapy, the bleeding continued at the site of the PICC insertion. Therefore, sequential therapy was performed and the bleeding was controlled.

Cases 2 and 3 were uncontrolled bleeding episodes following total knee replacements in both knees of a patient with hemarthropathy. In Case 2, the initial bypassing agent for the operation was rFVIIa, which was administered every 2 h at a dose of 90 µg/kg. At post-operative day 3, there was bleeding and swelling at the site of the operation. Hemoglobin and hematocrit were decreased to 5.3 g/dL and 14.8%, respectively. Since the bleeding was unresponsive to rFVIIa therapy, the bypassing agent was changed to APCC, which was administered every 12 h at a dose of 100 IU/kg

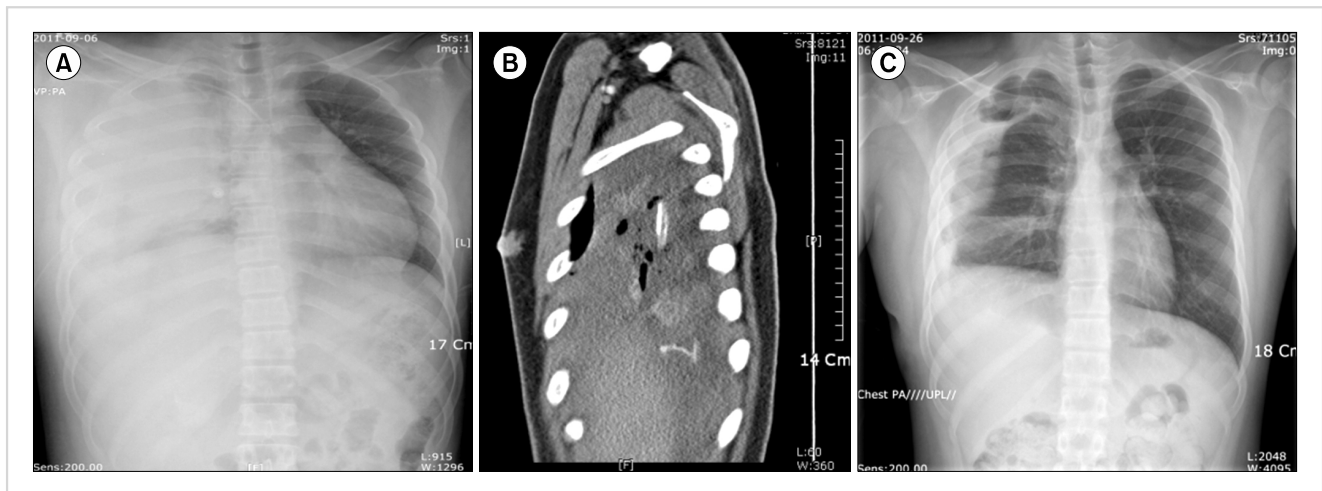
**Table 1.** Clinical characteristics of patients.

Case no.	Age (years)	Hemophilia	Inhibitor level (BU)		Previous prophylaxis with any bypassing agent
			Peak	At admission	
1	8	A, severe	1,126	160	No
2	37	A, severe	21	2	No
3	38	A, severe	21	Borderline	No
4	41	A, severe	120	4	No
5	15	A, severe	760	200	Yes

**Table 2.** Refractory bleeding episodes and previous unsuccessful treatment.

Case no.	Site or context of unresponsive bleeding	Previous unsuccessful treatment	Bleeding control after sequential therapy
1	PICC insertion	APCC 100 IU/kg×2 → rFVIIa 180 µg/kg/3 h×2	Yes
2	Total knee replacement	rFVIIa 90 µg/kg/2 h×6 → APCC 100 IU/kg/12 h×2	Yes
3	Total knee replacement	rFVIIa 90 µg/kg/2 h×4 → APCC 65 IU/kg/8 h×3	Yes
4	Small bowel obstruction	APCC 65 IU/kg/8 h×3 → rFVIIa 90 µg/kg/2 h×4	Yes
5	Hemothorax	APCC 65 IU/kg/8 h×2 → rFVIIa 90 µg/kg/2 h×3	Yes

Abbreviations: PICC, peripheral inserted central catheter; APCC, activated prothrombin complex concentrates; rFVIIa, recombinant factor VIIa.



**Fig. 1.** (A) Chest radiograph that shows a right hemothorax and an enlarged cardiac silhouette; (B) Chest CT that shows a hemopneumothorax with active bleeding; (C) Chest x-ray that shows a residual hemothorax after sequential therapy.

until the bleeding was controlled. On post-operative day 5, the treatment was changed back to rFVIIa, with a dose of 90  $\mu\text{g}/\text{kg}$  administered every 2 h, because the patient complained of bleeding and the knee was swollen again. After this change, the bleeding was controlled; however, another bleeding episode occurred on post-operative day 10. The patient was treated with sequential therapy and the bleeding was controlled. One year later, this patient underwent total knee replacement on the contralateral knee (Case 3). The treatment again had to be changed from single agent to sequential therapy because refractory bleeding occurred after the operation. The bleeding was controlled after sequential bypassing therapy.

The Case 4 patient complained of abdominal pain for 2 days and an abdominal computed tomography (CT) scan confirmed bowel ischemia by obstruction. Segmental resection of the small bowel was performed, and APCC was administered every 8 h after the operation at a dose of 200 IU/kg/day. Two days post-operation, bleeding was uncontrolled and disseminated intravascular coagulation (DIC) developed. The PT/aPTT were prolonged (18.8 second (INR 1.67)/126.3 second), D-dimer level increased to 2.5  $\mu\text{g}/\text{mL}$ , antithrombin III concentration decreased to 51%, and the platelet level was 29,000/ $\mu\text{L}$ . Antithrombin III and fresh frozen plasma (FFP) were used for DIC management and the bypassing agent was changed to rFVIIa. Abdominal CT showed active bleeding in the resection site and a re-operation was performed. The patient complained of hematemesis 7 days after the re-operation. Hemoglobin and hematocrit were decreased to 6.5 g/dL and 18.6%, respectively, and active bleeding was confirmed at the anastomotic site by abdominal CT. Yet another operation was performed and the patient was given sequential therapy, which successfully controlled the bleeding problem.

The Case 5 patient presented with complaints of right chest wall pain and fainted. Hemothorax was confirmed by chest radiography (Fig. 1A). The initial hemoglobin and

**Table 3.** Sequential bypassing therapy regimens.

Hour	Regimen 1 (Cases 1, 2, 3, 4)	Regimen 2 (Case 5)
0	APCC 100 IU/kg	APCC 65 IU/kg
4	rFVIIa 90 $\mu\text{g}/\text{kg} \times 1-2$	rFVIIa 90 $\mu\text{g}/\text{kg}$
8	APCC 100 IU/kg	APCC 65 IU/kg
12	APCC 100 IU/kg	rFVIIa 90 $\mu\text{g}/\text{kg}$
16	rFVIIa 90 $\mu\text{g}/\text{kg} \times 1-2$	APCC 65 IU/kg
20	rFVIIa 90 $\mu\text{g}/\text{kg} \times 1-2$	rFVIIa 90 $\mu\text{g}/\text{kg}$
24	APCC 100 IU/kg	APCC 65 IU/kg

Abbreviations: APCC, activated prothrombin complex concentrates; rFVIIa, recombinant factor VIIa.

hematocrit levels were 9.1 g/dL and 27.3%, respectively, and the platelet count was 233,000/ $\mu\text{L}$ . Initial fibrinogen was normal (249 mg/dL) and the D-dimer level had increased to 1.6  $\mu\text{g}/\text{mL}$ . We inserted a chest tube and administered APCC. Over 500 mL of blood was drained through the chest tube; however, the bleeding was not controlled. Follow-up laboratory tests showed the D-dimer level had increased to 2.4  $\mu\text{g}/\text{mL}$  and the platelet count had decreased to 146,000/ $\mu\text{L}$ . Therapy was changed from APCC to rFVIIa because of the bleeding, but the bleeding was not controlled and the patient experienced tachypnea and hypotension. A chest CT revealed a large amount of hematoma and active bleeding in the adhesion site (Fig. 1B). Following the patient's emergency electrocautery coagulation operation with sequential therapy, vital sign stabilized and bleeding was controlled (Fig. 1C).

The two sequential therapy regimens used in this study are displayed in Table 3. APCC was administered every 8 to 12 h. Maximum total daily dose of APCC was 200 IU/kg and the median single dose was 80 IU/kg (range, 65–100 IU/kg). rFVIIa was primarily administered between two APCC doses at a dosage of 90  $\mu\text{g}/\text{kg}$ . Bleeding was controlled

within 12 h of sequential therapy in all patients. Initial sequential therapy was discontinued after a median of 2 days (range, 1–4 days). After sequential therapy, a single bypassing agent was administered (APCC in Cases 1, 2, 4 and 5, and rFVIIa in Case 3) for 2 to 14 days. Sequential therapy was well tolerated by all of the patients. No adverse clinical events were recorded and neither thromboembolism nor DIC were observed.

## DISCUSSION

The development of an alloimmune antibody that inhibits FVIII or FIX currently represents the most serious complication for a person with hemophilia, particularly if the antibody has a high response classification [2, 3]. Approximately 30% of patients with hemophilia A and 1–3% of patients with hemophilia B will develop an inhibitor that makes treatment with conventional factor replacement ineffective [10, 11]. Two bypassing options are currently available and have been shown to be safe and efficacious for treating bleeding episodes in patients with inhibitors. Both agents, APCC and rFVIIa have demonstrated efficacy in treating bleeding in patients with inhibitors; however, some bleeding episodes do not respond well to either agent when used as a monotherapy [6, 7]. These unresponsive bleeding episodes are often very difficult to treat and can result in significant morbidity. A recently published consensus guideline for unresponsive or refractory bleeding in patients with high responding inhibitors recommends re-evaluating the treatment response every 8 to 12 h for the first day and every 24 h thereafter for limb threatening bleeding, and every 2 to 4 h for life-threatening bleeding [6]. If symptoms worsen or the patient does not improve, the treatment dose or frequency of dosing should be increased. At subsequent evaluations, if symptoms continue to worsen, additional changes in treatment are recommended such as switching products, increasing the dose or frequency of the current product, using sequential therapy, or using salvage therapies. Patients can experience various responses to either bypassing agent in different situations. Several studies suggest that response to treatment can depend on factors specific to each bleeding episode in each patient, such as the location or severity of the bleeding, a patient's age, and the presence of a target joint [6, 12–15]. Studies that used laboratory measurements to monitor response to bypassing agents have provided evidence that hemostatic responses vary in these patients. These studies have shown there are variations in thrombin formation or other clotting parameters after a bypassing agent is administered [13, 16]. In general, it might be difficult to predict responsiveness to bypassing agents. Another limitation is the lack of a reliable assay to measure potential responses to bypassing agents. A number of assays are available (for example, thrombin generation assay, thromboelastography, and clotting waveform analysis) that have potential to measure the efficacy of bypassing agents [17]. However, these assays have yet to be validated and each method has

advantages and disadvantages.

Our report and several other studies have demonstrated that hemostatic efficacy of sequential bypassing therapy is satisfactory. A major concern about sequential therapy is the risk of thrombosis, a well-recognized potential, but rare complication of both bypassing agents. Gringeri *et al.* reported on several cases of sequential therapies. The patients in their study had significant and progressive increases in D-dimer values post-therapy, along with decreases in platelet count and fibrinogen. These post-therapy laboratory values did not meet diagnostic criteria for DIC though [18]. Ingerslev and Sorenson, however, reported thrombotic complications following sequential bypassing therapy in patients who suffered from congenital hemophilia with inhibitors [5]. One case of fatal acute myocardial infarction occurred in the Ingerslev and Sorenson study [5]. In our study, there were no thrombotic events; one patient experienced DIC (Case 4), but improved. In Case 4 of our study, DIC developed due to uncontrolled bleeding and massive transfusion; however, the DIC resolved as bleeding was controlled by sequential therapy with antithrombin III and FFP.

In conclusion, this study showed that sequential bypassing therapy was efficacious for managing bleeding episodes that had been unresponsive to single bypassing therapy without clinically significant adverse events. However, thromboembolism may develop and risk of thrombosis must be considered. Patients should be hospitalized, and direct expert supervision is needed for adequate patient management. In addition, physical examination and frequent laboratory monitoring are necessary for early detection of thrombosis and DIC. Future research, in the form of prospective randomized trials, should be performed to prove the safety and efficacy of this approach for optimal management of refractory bleeding episodes.

## Authors' Disclosures of Potential Conflicts of Interest

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

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