Sequential therapy with activated prothrombin complex concentrate and recombinant factor VIIa in the treatment of unresponsive bleeding in patients with hemophilia and inhibitors in a single center experience

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Introduction

The development of inhibitors to factor VIII or IX is the most common, severe, challenging and expensive complication of the treatment of patients with hemophilia. Two bypassing agents are currently available and have been shown to be safe and efficacious in the treatment of bleeding episodes in patients with inhibitors : the anti-inhibitor coagulant complex FEIBA™ (FVIII inhibitor bypassing activity; Baxter AG, Vienna, Austria), and recombinant activated factor VIIa (rFVIIa; NovoSeven™, Novo Nordisk A/S, Bagsvaerd, Denmark). However, whichever treatment is used initially, 10–20% of bleeding events in haemophilia patients with high-responding inhibitors cannot be controlled by bypassing agents. Management of such bleeds is often difficult.

Method

This report describes the results of a retrospective review of 5 events of patients with severe hemophilia and inhibitors who have been treated with sequential doses of APCC and rFVIIa for refractory bleeding, and we inquired the efficacy and safety of the sequential therapy with APCC and rFVIIa in the management of bleeds unresponsive to a single bypassing agent. Sequential therapy was defined as the administration of both rFVIIa and APCC within 12 hours.

Results

In 5 events of 4 patients with inhibitor, bleeding was not controlled by initial bypassing treatment. Sequential therapy with APCC and rFVIIa was carried to all 5 cases with hemophilia A. Median age of ICH was 38 years old (range 8 – 41).

Table1. Clinical characteristics of patients

Patient No.	Age* (years)	Hemophilia	Inhibitor level* (BU)		Previous prophylaxis
			peak	at adm.	
1	8	A, severe	1126	160	No
2	37	A, severe	21	2.0	No
3	38	A, severe	21	Borderline	No
4	41	A, severe	120	4	No
5	15	A, severe	760	200	Yes

Table 2. Bleeding events and previous unsuccessful treatment.

Patient No.	Site or context of unresponsive bleed	Previous unsuccessful treatment
1	PICC insertion	APCC 100 IU/kg x 2 → rFVIIa 180 μg/ kg /3 hr x 2
2	Total knee replacement	rFVIIa 90 μg/ kg /2 hr x 6 → APCC 100 IU/kg/12 hr x 2
3	Total knee replacement	rFVIIa 90 μg/ kg /2 hr x 4 → APCC 65 IU/kg/8 hr x 3
4	Small bowel obstruction	APCC 65 IU/kg/8 hr x 3 → rFVIIa 90 μg/ kg /2 hr x 4
5	Hemothorax	APCC 65 IU/kg/8 hr x 2 → rFVIIa 90 μg/ kg /2 hr x 3

First patient had historical peak inhibitor titer increased to 1126 BU. During peripheral inserted central catheter insertion for ITI, bleeding was not controlled. After APCC and rFVIIa were administered sequentially, bleeding was controlled. The second and third patients had bleeding problems after total knee replacement for hemophilic arthropathy, and two agents were administered sequentially. The fourth patient had small bowel resection because of intestinal obstruction, and post-operation bleeding was not controlled well. DIC was developed after massive tranasfusion. Two agents were administered sequentially for bleeding problem and bleeding and DIC were controlled. The last patient had traumatic hemothorax.

Bleeding control was achieved in 12–24 h in all patients. Sequential therapy was discontinued after after median of 2 days (range 1-4 days). No clinical adverse events were observed.

Table 3. Sequential bypassing therapy schemes used.

hour	Regimen 1	Regimen 2
0	APCC 100 IU/kg	APCC 65 IU/kg
4	rFVIIa 90 μg/ kg x 1 ~2	rFVIIa 90 μg/ kg
8		APCC 65 IU/kg
12	APCC 100 IU/kg	rFVIIa 90 μg/ kg
16	rFVIIa 90 μg/ kg x 1~ 2	APCC 65 IU/kg
20		rFVIIa 90 μg/ kg
24	APCC 100 IU/kg	APCC 65 IU/kg

Conclusion

Sequential therapy with APCC and rFVIIa was efficacious in children and in adults without adverse events. A prospective clinical trial is needed to provide further evidence.

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