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Case Report
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Continuous Infusion of Turoctocog Alfa in Patients with Mild to Moderate Hemophilia A: A Case Series

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Case Report

Exogenous Factor VIII (FVIII) replacement therapy is used to control bleeding and maintain hemostasis in patients with hemophilia A. In most cases of severe bleeding or surgery, factor concentrate products require two to three times daily bolus dosing to maintain goal trough FVIII levels. Unfortunately, intermittent dosing can be operationally burdensome and difficult to tailor to individual patients, placing them at increased risk for bleeding and thromboembolism. To optimize the use of factor products, administration via continuous infusion has been used in place of traditional bolus or intermittent infusions. While guidelines do not explicitly state the optimal administration method, advantages to a continuous infusion strategy include the avoidance of peaks and troughs, and potential for cost savings due to a reduction in the total dose used to achieve hemostasis [1]. Use of continuous infusion factor concentrates has been most described in the perioperative setting, though it may also be considered to attain hemostasis in acute major bleeding episodes [1].

Hemostasis in hemophilia patients is achieved by increasing plasma concentrations of the deficient coagulation factor to a minimum identified in the World Federation of Hemophilia guidelines [1]. However, the use of many blood factor concentrates in continuous infusion may be limited by short beyond-use dating, often two to four hours after preparation. Clinicians and investigators can explore the possibility of extended use dating which may facilitate continuous infusion. Therefore, reporting clinical experiences with CI of factor products is important to promote consideration and adaptation of this practice.

Turoctocog alfa (NovoEight, Novo Nordisk, Denmark) is a third generation, beta domain-truncated recombinant FVIII product approved by the United States Food and Drug Administration in 2013 for on-demand treatment of bleeding episodes, perioperative management, and routine prophylaxis of bleeding episodes in adults and children with hemophilia A [2]. A prior report established stability of up to 10 h after product preparation; the authors then applied beyond use dating to facilitate CI in a surgical setting [3]. Here we further validate the previously reported stability experience and describe the utilization of CI turoctocog alfa.

At the time of our cases of CI administration, we collected the indication for factor supplementation, the desired FVIII activity level range, and FVIII activity levels recorded during the infusion. Clinical utility was assessed by calculated percent time in therapeutic range (defined as the number of levels drawn in range divided by the total number of FVII levels drawn during the infusion), and number of bolus doses needed for reasons other than discharge transition. At the time of utilization, turoctacog alfa was a recombinant factor VIII product on the inpatient formulary

Table 1: Patient characteristics.

Patient	Age	Gender	Diagnosis	Baseline FVIII Activity
1	46	female	Moderate hemophilia A	4%
2	58	Male	Mild hemophilia A	20%
3	45	male	Mild-moderate hemophilia A	3%

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Table 2: Patient bleeding presentation and CI factor experience.

Patient	Indication	Desired FVIII activity range (%)	Minimum FVIII activity recorded (%)	Maximum FVIII activity recorded (%)	Percent time in desired range (%)	Number of bolus infusions given with CI
1	Left thigh hematoma	80-100	55	229	44	1
2	Post-operation	80-100	52	85	33	1
3	Post-operation	80-100	51	153	54	2

and preference in managing and preventing acute bleeding events in hemophilia A patients. Based on the prior report by Takeyama et al. prepared factor was given a ten-hour expiration, therefore syringes were timed to exchange every six to eight hours [3]. Eventually beyond use was extended to 24 h, allowing for greater operational flexibility. Dosing and dose adjustments were made on a weight-based rate basis along with intermittent bolus doses based on FVIII activity responses [4].

Three patients were treated with continuous infusion administration of turoctocog alfa. Two patients were male and one female with an average age of 50 years, characteristics of each patient and their CI experience described in Table 1 and 2. All patients had a diagnosis of mild to moderate hemophilia A without history of inhibitor development. Two patients received turoctocog alfa infusion as perioperative treatment and one patient received treatment for a left thigh hematoma. Continuous infusion treatment was administered for an average of 5 days (3-8 days) at a rate of 4 IU/kg/h in two patients and 3 IU/kg/h in the third patient. Baseline FVIII activity ranged from 3% to 20% and desired FVIII activity throughout the infusion was 80% to 100% for each patient. Percent time in range of desired activity level was 33%, 44% and 54%. The average minimum FVIII concentration was 53% and average maximum was 156%. Patients required 1 to 2 bolus injections of FVIII product during the course of continuous infusion. None of the patients experienced excessive bleeding or inhibitor development. One patient developed a superficial vein thrombosis at an IV access site. This event occurred after FVIII levels unexpectedly rose above 200% as hemostasis was achieved and the patient's hematoma was resolving.

The safety and efficacy of turoctocog alfa is supported by the data from the Guardian trials; however, turoctocog alfa was administered only as a bolus injection in those studies [5-7]. While reports of CI second-generation beta domain-truncated and other non-beta domain-truncated third generation rFVIII products exist, they are dominated by cases occurring in the operative setting [8-10]. Similarly, there is a single case report detailing the use of CI turoctocog alfa in a patient with hemophilia A undergoing orthopedic surgery [3]. This group has more recently identified that the physical and chemical stability of this factor VIII product is maintained during CI over a 24-h period in the *in vitro* setting, therefore making turoctacog alfa administration by CI more feasible [4].

This report describes the successful use of CI turoctocog alfa for management of an acute severe bleed in one case and in the perioperative setting in two separate cases. In the case of an acute bleed, our patient's massive hematoma was effectively managed with continuous infusion FVIII replacement with turoctocog alfa during her hospitalization. As expected, given the patients bleeding status maintaining goal factor levels were difficult, however the use of CI administration maintained a basal level that could be supplemented with bolus doses as the CI rate was increased. The strategy effectively prevented worsening of bleeding events and allowed for quick dose adjustments without factor levels dropping too low which we felt optimized the patient's management. The patients in which CI turoctacog alfa was used in the postoperative setting were similarly managed and effectively achieved hemostasis after surgery. Our cases offer guidance on the use of CI administration in both acute bleeding and the postoperative setting and suggest that turoctacog alfa may be used effectively in these settings.

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