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CASE REPORT

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Congenital haemophilia A with inhibitor treated with recombinant factor VIIa in an infusion pump

Wiktoria Ryżewska [1], Michał Witkowski [2], Tadeusz Robak [2, 3]

[1]Students' Scientific Circle at the Department of Haematology of the Medical University of Łódź, Poland
[2]Department of General Haematology, Copernicus Memorial Hospital, Łódź, Poland
[3]Hematology Clinic, Medical University in Łódź, Poland

Summary

Congenital haemophilia A is a rare disorder where low factor VIII activity is the result of gene defect. Human coagulation factor VIII concentrate is used to prevent bleeding or for therapy.

The main therapy-related complication is development of an inhibitor against Factor VIII. Inhibitors are alloantibodies which neutralize procoagulant activity of exogenous factor VIII during replacement therapy. Bypassing agents are then the treatment of choice and can substitute factor VIII in maintaining haemostasis. Recombinant factor VIIa and activated prothrombin complex concentrates are of comparable effectiveness.

Significant numbers of haemophilia A patients with inhibitor are treated with recombinant factor VIIa. So far, it has been administered in bolus injections every 2 to 12 hours. Infusion pump is a promising alternative to bolus injections. Delivery of recombinant factor VIIa in an infusion pump has been proved effective in terms of maintaining accurate drug levels as well as minimizing human errors by reducing burden on staff.

Keywords: haemophilia A with inhibitor; infusion pump; recombinant factor VIIa

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Introduction

Congenital haemophilia A (HA) is a rare disorder. Factor VIII (FVIII) activity is low because of gene defect which is the cause of severe bleedings that manifest as extensive subcutaneous or mucosal hematomas, haemorrhages to joints or prolonged bleeding from wounds after invasive procedures [1–3]. The severity of bleeding disorder is correlated with FVIII activity in plasma. Patients usually have a history of bleeding prior to diagnosis and due to FVIII deficiency, they usually present isolated prolonged activated partial thromboplastin time (APTT) [4]. Replacement therapy with plasma-derived or recombinant Factor VIII concentrate is used for therapy and prophylaxis.

The main treatment-related complication in HA patients is the development of inhibitors — alloantibodies neutralizing the pro coagulant activity of exogenous FVIII during replacement therapy [5].

Therapy for HA patients with inhibitor has two main targets: restore and sustain haemostasis and induce immune tolerance to FVIII by eradicating the inhibitor. Bypassing agents, such as recombi-

Correspondence address: dr n. med. Michal Witkowski, Department of Genaral Hematology, Copernicus Memorial Hospital, ul. Pabianicka 62, 93–513 Łódź, Polska; tel: +48.426 895 191, e-mail: michal.witkowski@fundacja.hematologiczna.org
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nant factor VIIa (rFVIIa) or activated prothrombin complex concentrates (aPCC) are most frequently used for haemostatic treatment [6, 7]. More recent studies suggest that recombinant porcine factor VIII can be used for HA patients with inhibitor [8]. Its administration can be monitored with one-stage clotting assays — i.e. FVIII — based assays [4, 6].

Emicizumab, a bispecific antibody, which can bind to both factor IXa and X and does not require FVIII, can only be used in HA adults for prevention of bleeding [9, 10].

Eradication of the inhibitor is achieved by delivering immunosuppressants such as prednisone, cyclophosphamide or rituximab [4].

The *in vivo* half time of bypassing agents such as rFVIIa, is 2.8 h [11]. So short a time requires frequent bolus injections. Infusion pump instead of bolus injections is not only a more efficient solution, but also more accurate as it helps to maintain a constant level of the bypassing agent [11–13].

We describe here a case of a 56-year-old patient with severe congenital haemophilia A with inhibitor developed after a week of successful FVIII replacement therapy. The patient was treated with rFVIIa drlivered through an infusion pump.

Case presentation

A 56-year-old male patient with severe congenital hemophilia A was admitted to the Department of General Hematology after an episode of extensive spontaneous bleeding to subcutaneous tissue of the thorax and pleural cavities (Fig. 1).

The patient had a history of epilepsy, hypertension and Upon admission, haemoglobin (Hgb) was 5.6 g/dL (12.1–17.0), activated partial thromboplastin time (aPTT) 92 s (25.4–36.9). There were no signs of thrombocytopenia, international normalized ratio (INR) and thrombin time (TT) were within normal range. The level of FVIII was below 1%.

Gastroscopy revealed previous bleeding from the upper gastrointestinal tract — as well as blood clots in stomach and hemolysis, no active bleeding. Thorax CT showed fluid in the right pleural cavity (64 mm) and heterogeneous hematoma (124 × 83 × 178 mm) in the pectoral muscles on the right side with reactive thickening/edema of the surrounding subcutaneous tissue.

The patient was on hemostatic treatment with plasma-derived coagulation factor VIII concentrate. On the first day of hospitalization, he was given 9500 IU of FVIII concentrate intravenously (first 4500 IU, then 2500 IU twice at 8-hour intervals). During the next 3 days, the patient was given 2000 IU of FVIII concentrate intravenously every 12 hours. On day 7, bleeding became more intense. FVIII level decreased to below 1% and aPTT was prolonged to 84.8 s. Inhibitor titer against human factor VIII was 993 BU /ml (normal < 0.5 BU /ml). aPCC was administered (5000 IU intravenously every 12 hours); the bleeding was arrested and the patient's overall condition improved.

After 16 days of successful therapy, aPCC was reduced to 5000 IU daily. A peripheral inserted central catheter (PICC) was supposed to facilitate outpatient administration of coagulation factor. PICC was complicated by hematoma of the left arm with pressure on adjacent tissues which manifested with finger numbness. The patient's condition was consulted with a vascular surgeon, as well as the anesthesiologist who performed PICC. Surgery was performed after restoring hemostasis with 7000 IU of aPCC.

After surgery, the patient's Hgb was 10.2 g/dL, aPTT 122 s (25.4–36.9). INR and TT were within normal. The level of factor VIII (FVIII) was below 1%. Patient's response to aPCC after surgery was unsatisfactory. For better bleeding control, the treatment was switched to rFVIIa (eptacog alfa) delivered in an infusion pump at a dose of 90 μg/kg in boluses every 3 hours for 3 days and then every 6 hours for 3 days, twice daily for 2 days and once daily for 11 days.

The patient was discharged from the Department of General Hematology in satisfactory overall

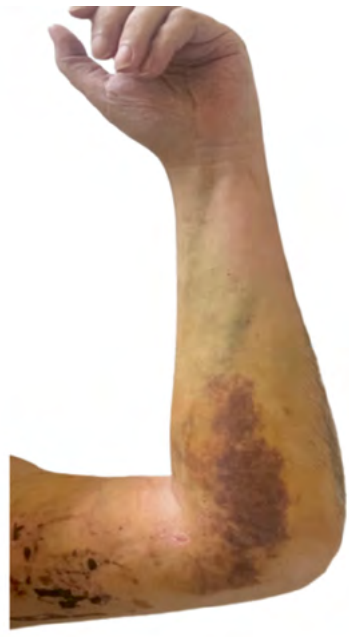

Figure 1. Extensive ecchymosis of the left upper limb

condition, with indication to take 8 mg of eptacog alfa once daily for 4 days, then 8 mg every second day until healing of thoracic wound.

Because of problems with venous access and insufficient response to aPCC (rVIIa is not registered for prophylactic treatment), we applied for emicizumab to the National Blood Center.

Discussion

Rapid and appropriate therapy for HA patients with inhibitor is crucial especially when bleeding is severe and the decrease in haemoglobin significant. Replacement therapy with rVIIa or APCC is administered to sustain haemosthasis in HA patients with inhibitor [14]. A relatively new treatment option is recombinant porcine FVIII (rpFVIII).

Human FVIII (hFVIII) can be administered in exceptional cases, particularly when bypassing agents are not immediately available [15]. Nevertheless, this therapy is only effective for patients with low inhibitor titers (< 5 BU) [16]. Patients with high inhibitor titers can benefit more from replacement therapy [15].

The safety profile of recombinant porcine FVIII (rpFVIII) is better while the biochemical and hemostatic properties are similar [17]. Effectiveness of either human or recombinant porcine FVIII depends on the presence or absence of alloantibodies against those factors. Some patients' response to rpFVIII depends on the cross-reactivity between FVIII inhibitor and rpFVIII [18].

EACH 2 study concluded that effectiveness of first-line treatment with aPCC is similar to that of rFVIIa [19]. The study also showed that rFVIIa was the most widely used haemostatic agent. However, the cost-effectiveness models for both bypassing agents are in favour of aPCC. Kim et al. concluded that for high-titered bleeding patients, aPCC is a much more cost-effective treatment strategy compared to rFVIIa [20]. This suggests that aPCC may be considered in HA patients, if there are no clinical contraindications.

HAVEN studies have shown emicizimab — a recombinant, humanized, bispecific monoclonal antibody — to effectively prevent bleeding in HA patients with or without inhibitor [21–23]. Emicizimab is administered subcutaneously, which is a convenient alternative for patients with difficult venous access or with limited options for bleeding prophylaxis [22]. It is also suitable for outpatient administration. Its major limitation are cost and accessibility. In Poland, it can only be delivered to HA patients with inhibitor. Criteria for qualifying patients for long-term bleeding prophylaxis with emicizumab are defined and limited by the National Drug Program [24].

Our patient was on rFVIIa therapy due to the lack of response to aPCC or no immediate access to emicizumab. The decision to administer rFVIIa in an infusion pump was motivated by recent studies presenting benefits of this method of drug delivery as compared to intermittent bolus injections [25, 26]. The use of infusion pump facilitates accurate dosage of the drug which leads to cost reduction as well as improvement of the patients quality of life [27]. Infusion pump reduces overall nursing time of HA patients with rFVIIa from 3–5 hours to 1–2 hours a day, which is desirable in terms of reducing the burden on the nursing staff and minimizing the risk of human error [27, 28].

We have conducted a survey amongst the nursing staff of the Department of General Hematology in Łódź (n = 10). Nurses were asked to indicate their preferred way of rFVIIa administration as well as to assess the level of difficulty of working with both bolus injections and infusion pump. The results of the survey are presented on Figures 2 and 3. Of the responding nurses, 70% indicated the infusion pump as preferable to bolus injection; 70% described infusion pump administration as relatively easy (3 out of 5 points or more).

Conclusions

For HA patients with inhibitor, the effectiveness of aPCC and rFVIIa therapies is comparable.

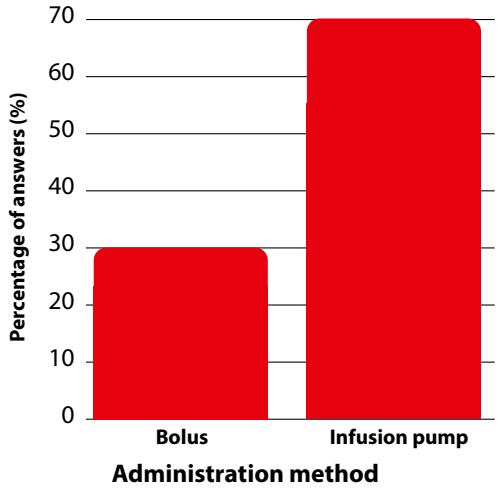

Figure 2. Graph depicting the nursing staff's preferences of recombinant factor VIIa administration. The x axis corresponds to the administration method. The y axis indicates the percentage of answers

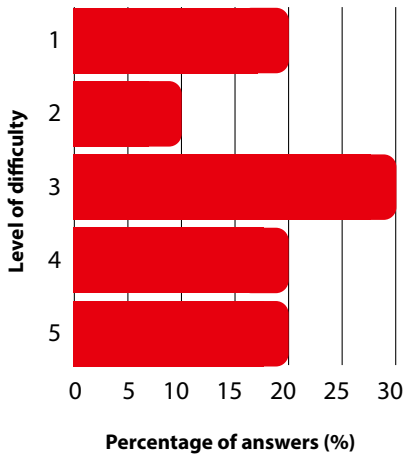

Figure 3. Graph presenting level of difficulty of recombinant factor VIIa administration by infusion pump assessed by the nursing staff. The x axis is the percentage of answers. The y axis is the level of difficulty (from 1— very easy to 5 — very difficult)

A significant number of HA patients with inhibitor can be administered rFVIIa in an infusion pump which has advantage over intermittent bolus injections. This option cuts down on expenses as well as contributes to improvement of patient's quality of life while maintaining accurate drug dosage. It also reduces the burden on the nursing staff and thus minimizes the risk of human error. According to our survey, this method of drug administration is preferred by the nursing staff.

Conflict of interest: The authors disclosed no conflicts of interest.

Authors contributions: MW, and TR suggested the idea of the case report. MW took care of the patient. WR, MW contributed to writing the article. All authors (WR, MW, TR) contributed to manuscript revision.

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