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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Benefits of infusion pump technology in treatment of patients with acquired hemophilia A and hemophilia A with inhibitor a Polish pilot observational study

Michal Witkowski[1, 2*], Wiktoria Ryżewska[2, 3], Tadeusz Robak[4]

[1]Department of Hematology, Copernicus Memorial Hospital, Lodz, Poland
[2]Foundation For Helping Patients With Leukemia, Lodz, Poland
[3]Jozef Stus Memorial Multispecialty Municipal Hospital, Poznan, Poland
[4]Hematology Clinic, Medical University in Lodz, Poland

Abstract

Introduction: The authors compared the efficacy, practicality and personnel preference of the infusion pump method against those of bolus administration of rFVIIa.

Material and methods: Three patients with hemophilia A received recombinant factor VIIa infusion pump treatment. Their hemostasis and response to treatment was strictly monitored. Nursing personnel (n = 20) were surveyed on their preference and opinion regarding the infusion pump compared to bolus administration of recombinant factor VIIa.

Results: The maintenance of hemostasis was satisfactory in the group of patients who were administered recombinant factor VIIa via infusion pump, and no dosage was missed or delayed. A large majority of the surveyed personnel (75%) evaluated the infusion pump as offering a more comfortable and easier administration method than 4-hourly boluses.

Conclusions: Recombinant factor VIIa via infusion pump is more effective in maintaining hemostasis and is the preferred administration method among nursing personnel. Patients and personnel alike benefit from infusion pump administration of recombinant factor VIIa for hemophilia A.

Keywords: hemophilia A, acquired hemophilia A, inhibitor, recombinant factor VIIa, infusion pump

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Introduction

Hemophilia A (HA) is a congenital or acquired bleeding disorder characterized by deficiency or dysfunction of coagulation protein factor VIII (FVIII). Congenital hemophilia A (HA) is a recessive genetic disease of adult males and boys caused by mutation in the F8 gene on the X chromosome [1]. Acquired hemophilia A (AHA) is a very rare bleeding disorder, with an estimated incidence of 1.48 per million per year [2]. Unlike HA, AHA is an autoimmune disease caused by spontaneous production of autoantibodies against clotting factor VIII (FVIII), and it occurs in both men and women [3]. The typical clinical manifestation of AHA includes sudden onset of bleeding in a person with no personal or family history of hemorrhages [4, 5]. AHA is a severe hemorrhagic disorder manifesting with bleeding events of differing severities. In contrast to HA, there is no strict relationship between the activity of FVIII in plasma

*Address for correspondence: Michal Witkowski
Department of Hematology, Copernicus Memorial Hospital,
Pabianicka 62, 93–513 Lodz, Poland;
e-mail: michal.witkowski@fundacja.hematologiczna.org

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and the severity of hemorrhagic diathesis in AHA patients [6]. About 30% of AHA patients initially experience minor bleeding, while others can suffer from life-threatening hemorrhages [3].

The most common symptoms of HA include muscle hematomas and intra-articular bleeding, while those of AHA include subcutaneous hemorrhages, mucosal bleeding, retroperitoneal bleeds, and prolonged bleeding after surgical procedures [1–3].

In more than 30% of patients with severe HA (defined as FVIII activity of less than 1 international unit (IU)/dL) and 3–13% of patients with moderate and mild hemophilia (FVIII activity of 1–5 IU/dL and >5–40 IU/dL respectively), inhibitor to FVIII will develop [7]. Inhibitors are alloantibodies to FVIII that typically neutralize factor VIII activity and thus also the function of infused clotting factor concentrates [8]. The occurrence of FVIII inhibitor currently represents the most serious complication of hemophilia A [9]. In the presence of these inhibitors, bleeding generally does not respond to replacement therapy using concentrates of the deficient clotting factor [7].

The treatment of HA typically involves regular infusions of factor VIII concentrates to prevent bleeding episodes, with doses adjusted based on the severity and individual responses [10]. The therapeutic approach for AHA is based on three key principles: stopping the bleeding, initiating immunosuppressive therapy to eliminate the inhibitor, and addressing any underlying condition identified [11]. The most effective treatment of AHA-related bleeding is the administration of by-passing agents (BPAs) such as recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (aPCC), or recombinant porcine factor VIII (rp-FVIII) [12]. BPAs are also indicated in HA in patients with inhibitor titers higher than 10 Bethesda Units (BU)/mL, along with immune tolerance induction (ITI) [13].

rFVIIa (eptacog alpha) is given at a dose of 90 µg/kg every 2–3 hours as a 2–5 minute intravenous bolus. The interval between doses can be extended to 4, 6, 8 or 12 hours based on the severity of the bleeding [6, 14]. The frequency of bolus injections is a result of the short half-time of rFVIIa, which is 2.8 hours *in vivo* [12]. There have been studies discussing the use of an infusion pump instead of bolus injections in HA patients [15–17]. According to the rFVIIa Summary of Product Characteristics (SmPC), the product remains stable for 24 hours at 25°C when stored in a 50 mL polypropylene syringe. This stability allows for intensive therapy with automatic rFVIIa boluses delivered via an infusion pump [6, 14].

Continuous infusion, as opposed to repeated bolus injections, is a more precise and time-efficient method of administration. It has the potential to reduce the burden on nursing staff and improve the patient's quality of life (QoL), as well as to reduce the overall cost of treatment [13, 14].

In this study, the authors compare the efficacy and practicality of, and personnel preference for, the infusion pump method against those of bolus administration of rFVIIa.

Aim of study

Comparison of efficacy and practicality of, and personnel preference for, infusion pump method versus those of bolus administration of rFVIIa.

Material and methods

The authors conducted a single-center prospective comparative study at the General Hematology Department, Copernicus Memorial Hospital, Lodz, Poland.

Patients

The study included patients with hemophilia A acquired (n = 2) or with inhibitor (n = 1) who received treatment with recombinant factor VIIa via an infusion pump. The efficacy of the treatment was assessed by monitoring patients' response to treatment and their adverse events profile.

Infusion pump

All three patients were administered eptacog alpha at dosage of 90 µg/kg. The drug was administered through a peripheral access on the arm. Prior to administration, patient weight was assessed and bolus intervals were set. The drug was not diluted and was kept in a 50 mL polypropylene syringe for no longer than 24 hours at room temperature.

Nurse evaluation

Highly-qualified nursing personnel who administered rFVIIa via infusion pump at the Department of General Hematology in Lodz (n = 20) were questioned on their preference and opinions regarding infusion pump compared to bolus administration of recombinant porcine factor VIII. This questionnaire consisted of seven questions (see Tab. I).

Results

Study group characteristics and patient outcomes

The study group consisted of three patients, two with AHA and one with HA with inhibitor. Detailed characteristics of the study cohort are set out in Tables II and III.

The authors present below case reports of the three patients who received rFVIIa infusion pump treatment.

Patient 1

A 74-year-old Caucasian female was referred to the Department of General Hematology in Lodz from a county hospital with suspicion of AHA, where she had been hospitalized due to sepsis. On admission, the patient had extensive

Table I. Questionnaire

Question 1	IV bolus administration every 4 hours	25%
Which method of administering hemostatic drugs (eptacog alpha, susoctocog alpha) do you think is more comfortable?	Supply in infusion pump replaced every 24 hours (boluses delivered automatically by pump)	75%
Question 2	1	35%
How would you assess the level of difficulty in the administration of recombinant porcine factor VIII concentrate as an intravenous bolus on a 24-hour basis?	2	15%
	3	20%
	4	15%
(1 = very easy, 5 = very difficult)	5	15%
Question 3	1	30%
How would you assess the level of difficulty in the supply of recombinant factor VIIa in an infusion pump replaced every 24 hours?	2	25%
	3	15%
(1 = very easy, 5 = very difficult)	4	15%
	5	15%
Question 4	Need for frequent administration at precise time intervals	20%
What do you think is the greatest difficulty in the administration of recombinant porcine factor VIII concentrate in an intravenous bolus?	Frequent blood sampling	30%
	Large number of vials administered at one time	35%
	Long preparation time	15%
	Other	0%
Question 5	Permanent connection of patient to infusion pump	55%
What do you think is the greatest difficulty in the administration of recombinant factor VIIa in an infusion pump?	Preparing medicine in syringe for infusion pump	20%
	Long preparation time	15%
	Other	10%
Question 6	Shorter daily duration of drug administration to patient	15%
What do you think is the biggest advantage of administering recombinant factor VIIa in the infusion pump?	Administering drug at precise time intervals	65%
	No need for frequent blood collection	10%
	Short preparation time	10%
Question 7	Possibility of monitoring concentration of factor	15%
What do you think is the biggest advantage of administering recombinant porcine factor VIII concentrate as an intravenous bolus?	Drug administration without use of an infusion pump	40%
	Patient is not permanently connected to infusion pump	45%

subcutaneous ecchymoses on the upper and lower limbs and lateral sides of the thorax. Laboratory studies revealed a prolonged activated partial thromboplastin time (aPTT) of 104.9 s (normal range 25.4–36.9 s).The level of factor VIII was less than 1% and inhibitor titer against human factor VIII was 4.9 j.B/mL(normal < 0.5 j.B/mL). The patient was started on treatment with eptacog alpha (0.09 mg/kg intravenously (i.v.) via an infusion pump with bolus intervals of three hours) and eradication of inhibitor via the use of prednisone (1 mg/kg per day). The treatment course was uneventful, and the rFVIIa administration was prolonged firstly to 4-hourly and then to 6-hourly intervals. The treatment was then followed by rpFVIII. Due to the development of anemia and increased demand for rpFVIII, aPCC was administered. The inhibitor eradication therapy was intensified with cyclophosphamide and later rituximab, resulting in elimination of the inhibitor and an increase in FVIII level. The treatment course, as well as the levels of inhibitor titer and FVIII, are depicted in Figure 1.

Table II. Characteristics of study group

Analyzed trait	Value (number of patients)
Type of hemophilia	
Acquired hemophilia A	2
Hemophilia A with inhibitor	1
Age at beginning of pump treatment	
50–60	1
61–70	0
71–80	1
81–90	1
Sex	
Female	1
Male	2
Disease at beginning of pump treatment	
New diagnosis	2
Relapse	1
Lines of treatment in this hospitalization	
1	0
2	2
3	1
Previous treatment	
Recombinant factor VIIa	2
Porcine factor VIII	1
Activated prothrombin complex concentrate	3
Inhibitor eradication	
Prednisone, rituximab, cyclophosphamide	2
No treatment	0
Bleeding score at diagnosis	
1	1
2	1
3	0
4	0
5	1
Bleeding score at beginning of treatment	
1	2
2	0
3	1
4	0
5	0

Table III. Laboratory parameters of study cohort

Laboratory parameters at beginning of pump treatment (value)	Value		
	Patient 1	Patient 2	Patient 3
Factor VIII level [%]	1%	<1%	<1%
Inhibitor titer (BU)	4.9	1,239	1
PLT (×10^3/μL)	343	226	204
APTT (s)	105	118	87
PT (s)	1.04	1	0.96
WBC (×10^3/μL)	13	10	10
HGB (g/dL)	8.3	9.8	8.7

Table IV. Comparison of infusion pump and bolus administration

Feature	Bolus administration	Infusion pump administration
Frequency of administration	Every 4 hours	Replaced every 24 hours
Precise time of administration	Depends on nursing staff	Depends on pump settings
Precise dosage administration	Impossible	Available
Time spent on administration	90 min/day	15 min/day
Iatrogenic sleep deprivation	Present	Not present
Burden on nursing staff	Heavy	Mild

Patient 2

An 86-year-old Caucasian male was admitted with extensive subcutaneous ecchymoses on both upper limbs and a suspicion of AHA. His laboratory studies revealed a greatly prolonged aPTT of 129 s (normal range 25.4––36.9 s), factor VIII level of less than 1%, and inhibitor titer of 1,331 BU/mL During hospitalization, hemostatic treatment was administered. Initially this took the form of recombinant factor VIIa using an infusion pump, then aPCC, resulting in disappearance of the symptoms of bleeding diathesis. At the same time, inhibitor eradication treatment was used (prednisone, cyclophosphamide, rituximab), achieving an improved clinical condition, a reduction of the inhibitor titer to 140 BU/mL, and an increase of FVIII level up to 26%. The patient's treatment course is depicted in Figure 1.

Patient 3

A 56-year-old male with severe HA was admitted after an episode of extensive spontaneous bleeding into the subcutaneous tissue of the thorax and pleural cavities.

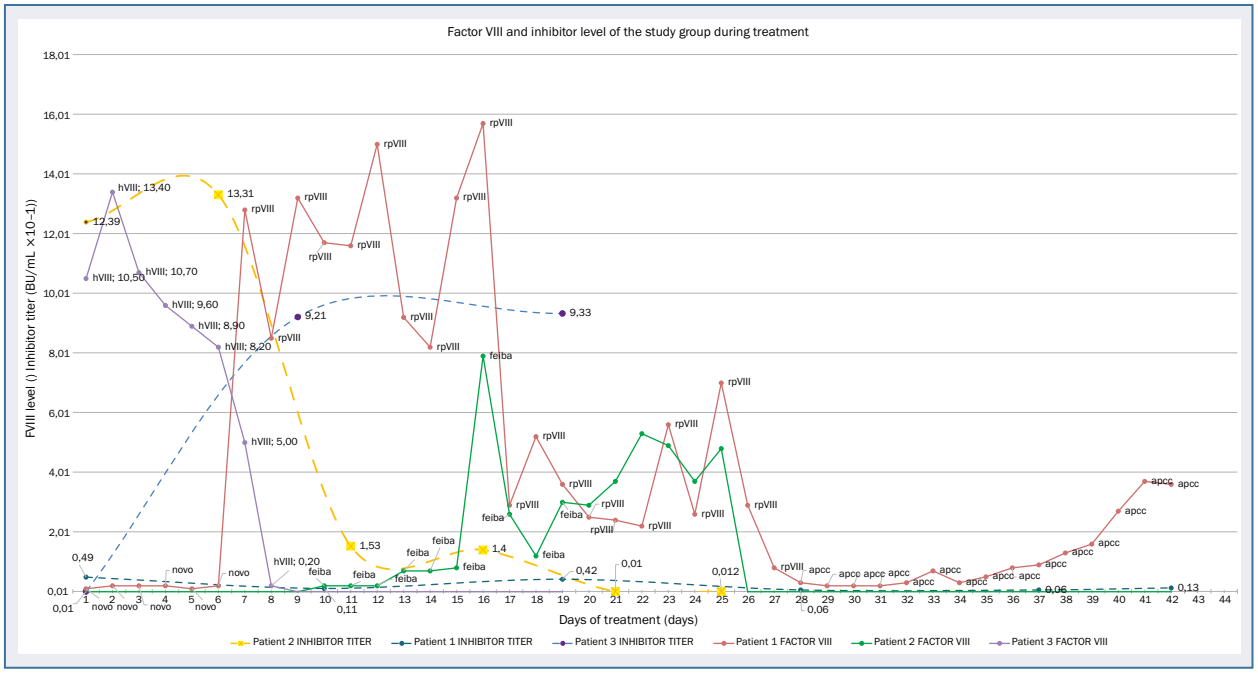

Figure 1. Laboratory parameters (factor VIII level, inhibitor titer) and course of treatment of study group (n = 3). APCC — activated prothrombin complex concentrate; hFVIII — human factor VIII; rFVIIa — recombinant factor VIIa; rpVIII — recombinant porcine factor VIII Solid lines represent level of factor VIII in patients 1 (blue), 2 (orange) and 3 (green). Dotted lines represent level of inhibitor titer, which was regularly monitored throughout treatment. Treatment course of study group is presented descriptively on graph. X axis represents days of treatment. Patient 1 had longest treatment course (43 days), Patient 2 had a treatment of 26 days, and Patient 3 had shortest treatment of 20 days.

On admission, the patient's aPTT was 92 s (normal range 25.4–36.9) and FVIII level <1%. He received hemostatic treatment with a plasma-derived factor VIII concentrate. On day 7, intensification of hemorrhagic diathesis was observed. FVIII again decreased to <1% and aPTT prolonged to 84.8s. Inhibitor titer was 993 BU/mL. aPCC was administered (5,000 IU intravenously every 12 hours), which resulted in the inhibition of bleeding and an overall improvement in his clinical condition. 16 days after uneventful aPCC treatment, the dosing interval was reduced to every 24 hours. In order to facilitate the outpatient administration of coagulation factor, the patient received a peripherally inserted central catheter (PICC) due to difficulties with access. Although the patient was prepared for the procedure (7,000 IU of aPCC), his response to aPCC after the procedure was unsatisfactory: his aPTT was 122 s, and FVII <1%. Therefore, his hemostatic treatment was switched to eptacog alpha in an infusion pump at a dosage of 90 µg/kg boluses every three hours for three days, and then every six hours for three days, twice a day for two days and once a day for 11 days. The patient was discharged from the Department of General Hematology in good general condition, with eptacog alpha 8 mg once a day for four days, then 8 mg every second day until the thoracic wound had healed. The patient's laboratory parameters and course of treatment are depicted in Figure 1.

Nurse evaluation outcomes

A large majority of surveyed personnel (75%) evaluated the infusion pump as a more comfortable and easier administration method than 4-hourly interval boluses. Only 35% claimed bolus injection treatment to be very easy, while 55% assessed infusion pump treatment as either very easy or easy. Among the greatest difficulties in bolus administration, the surveyed personnel identified frequent blood sampling (30%) and a large number of vials administered at the same time (35%), while 65% pointed to the precise time of drug administration as the greatest advantage of infusion pump administration. The greatest challenge in infusion pump treatment was considered by 65% of those surveyed to be the patient's constant connection to the infusion pump. This was also the only advantage of bolus injections named by the personnel.

Discussion

Several studies have explored the efficacy and safety of using rFVIIa administered via infusion pumps in hemophilia treatment, especially in a surgical setting [16, 18–21]. The first attempts to introduce rFVIIa infusion pump treatment came about in 1996 when Schulman et al. [18] evaluated the stability of rFVIIa in three different infusion systems. According to their study, continuous infusion with rFVIIa

was feasible and resulted in a reduction of the total dose of rFVIIa by 50–75%, depending on the behavior of the clearance. No contamination of the infusion systems was noted. However, the greatest challenge constituted thrombophlebitis at the infusion site, which was addressed by the addition of low-molecular weight heparin to an infusion bag [18]. In 2002, Stachnik et al. [20] concluded that continuous infusion of rFVIIa can enable the maintenance of constant factor concentration and thus reduce the risk of bleeding and reduce factor consumption. Over the following years, further research was conducted that came to the same conclusion [19–22]. In 2019, Négrier et al. [16] investigated the practicality and effectiveness of rFVIIa mini-pump treatment. They also conducted a survey among their nursing personnel, which revealed a preference for infusion pump administration over bolus injections [16].

Infusion pump is superior to bolus injections in terms of providing the patient with a safe and constant level of rFVIIa. Unlike the infusion pump, bolus injections require rounding the dosage of rFVIIa up or down to the nearest figure [17]. This is a crucial factor in terms of the treatment's cost-effectiveness. As long ago as 1993, Carlsson et al. [22] managed to establish an appropriate rFVIIa dose and dose interval for each patient that would allow for the maintenance of a trough factor concentration >1% at all times. They concluded that, if administered in a continuous infusion, the rFVIIa consumption would reduce to 22,000 units/year compared to 275,000 units/year with standard prophylactic dosing [22]. rFVIIa treatment is expensive: a single bolus for an 80 kg adult (a 7 mg dose) costs $9,514 [23]. The reduction of costs offered by infusion pump treatment is not only limited to fixed dosage administration; it is also more economical in the context of nursing care. According to Pollard et al., in the United Kingdom, rFVIIa bolus dosage administration takes c.6 nursing hours per 24 hours, yet when using the pump the time amounts to only one nursing hour per 24 hours [17].

Reducing nursing time from six hours to one is also desirable because it lessens the burden on the nursing staff and lowers the risk of human error [17, 21]. The results of our questionnaire reveal infusion pump to be the preferred method of administration among 75% of the surveyed nursing personnel. Rated its greatest advantage by 65% was the possibility of administering the drug at precise time intervals, while having large numbers of vials administered at the same time (35% of surveyed) and frequent blood sampling (30%) were identified as the greatest disadvantages of bolus injections.

The concerns regarding infusion pump therapy center on the stability of the drug, the risk of infection, the risk of development of phlebitis at the infusion site, the risk of pump failure, and the possibility of inhibitor development [19]. According to SmPC, rFVIIa remains stable for 24 hours at 25 °C when stored in a 50 mL polypropylene syringe. This stability enables infusion pump therapy [6, 14]. To date, there have not been any reports indicating early systemic infections complicating infusion pump treatment. Maintaining sterile conditions during preparation is crucial in preventing infection [19, 24–26]. Phlebitis was a common complication described in the initial studies documenting rFVIIa infusion treatment [18, 27]. Nowadays, this can easily be prevented by parallel infusion of saline [19]. The increasing quality of infusion pumps means that reports of pump failure are very rare. Frequent monitoring and thorough preparation prior to introduction of the pump treatment can be taken as preventive measures [19]. Kempton et al. [27] found no evidence of a link between constant infusion treatment and the development of inhibitors in patients with moderate or mild hemophilia who underwent intensive treatment for surgery. All reports of the development of inhibitor as a consequence of infusion pump treatment are anecdotal [19, 28, 29].

In the three patients treated in our Department, there was no compensation in hemostatic effect as a result of pump treatment. The course of management was uneventful, and no side effects were reported.

A comparison of infusion pump and bolus administration is set out in Table IV.

Conclusions

Recombinant factor VIIa via an infusion pump is more effective in maintaining hemostasis and is the preferred administration method among nursing personnel. Patients and personnel alike benefit from infusion pump administration of recombinant factor VIIa for hemophilia A.

Article information and declarations

Data availability statement

Data openly available in a public repository that issues datasets with DOIs.

Ethics statement

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals. Our study does not require any ethics committee approval. The authors acknowledge and declare that no breach of ethical rules has been made during the preparation and publication of the study.

Authors' contributions

MW — original idea for article, patient management; MW, WR — writing of article. All authors contributed to revising and editing the manuscript.

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Conflict of interest

The authors have disclosed no conflict of interest.

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