Home treatment of haemarthrosis with recombinant activated factor VII in patients with haemophilia A or B and inhibitors: experience from developing countries

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Home therapy for uncomplicated mild/moderate bleeding can decrease healthcare burden, promote self-esteem, reduce complications, and provide near-normal quality of life. To evaluate recombinant activated factor VII (rFVIIa) as home therapy for joint bleeds in Algeria, Morocco, Oman, Saudi Arabia, and United Arab Emirates. Twenty-seven patients aged more than 2 years with congenital haemophilia and inhibitors were monitored for up to 8 months after a first haemarthrosis episode treated with rFVIIa. Assessments were made by patients/caregivers with a standardized diary. The main measures included home-managed bleeds, haemostasis, and pain relief within 9 h after first injection. Additional analyses included convenience, time to pain resolution, and doses given within 48 h. Of 132 bleeds, 84 (63.6%) were managed at home. Of these, successful haemostasis (partial or complete) was achieved at 9 h in 87.8%, with pain relief for 84.0%. For all treatment settings, successful haemostasis at 9 h was achieved for 86.3% of bleeds, with pain relief achieved for 74.8% of bleeds. Higher initial dosing was associated with fewer injections. Median time to complete haemostasis was 48 h (spontaneous bleeds) and 24 h (traumatic bleeds). Median time to complete pain relief was 24 h for both bleed types. Satisfaction with treatment was high. No safety concerns were reported. Results from this observational study agree with previous data on the safety and efficacy of home treatment with rFVIIa and will help to increase awareness and aggregate experience, fostering confidence in home management of haemophilia patients with inhibitors in developing countries. *Blood Coagul Fibrinolysis* **28:145–151 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Management of haemophilia should include prevention of bleeding by implementing a programme of prophylaxis, early treatment of all acute bleeds with the appropriate factor concentrate, and the use of bypassing agents in patients with inhibitors. Although some bleeding episodes require treatment in a hospital or haemophilia treatment centre, home therapy should be used to manage uncomplicated mild-to-moderate bleeds [1].

Development of neutralizing antibodies to clotting factor (F) VIII or FIX occurs in up to 30% of patients with haemophilia A and 3% of patients in haemophilia B, respectively [2–4]. In these patients, standard therapy involves on-demand treatment with bypassing agents and attempts to eradicate the inhibitor. In developing countries, however, management of people with haemophilia with inhibitors is challenging because of the relative lack of specialist care and financial resources. In such countries, proper education and application of a supervised home-therapy strategy can reduce acute and chronic joint complications, promote self-esteem, allow patients to have a near-normal quality of life, and decrease hospital and financial burden [5]. Previous studies have demonstrated the feasibility of home treatment with recombinant activated FVII (rFVIIa) in developed countries [6–8].

The primary aim of the present study was to identify management practices using rFVIIa for joint bleeds, and

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their outcome, in patients with haemophilia and inhibitors in a home setting in countries of the developing world.

Methods

Study design

The study was an international, prospective, multicentre, observational study conducted in Algeria, Morocco, Oman, Saudi Arabia, and the United Arab Emirates, between October 2010 and April 2012 (ClinicalTrials.gov: NCT01234545). No randomization, stratification, or blinding was performed.

Each participant was observed for 8 months of treatment – beginning with the first bleeding episode reported by the patient – followed by a final visit. To ensure an adequate number of bleeds from a suitable number of patients, patients were withdrawn if no bleed had been registered within 2 months. The maximum duration of the study for each patient was therefore 10 months.

Haemarthrosis was treated with rFVIIa (NovoSeven; Novo Nordisk A/S, Denmark). Two rFVIIa regimens are licensed for the treatment of mild-to-moderate bleeds – 90 μg/kg every 2–3 h, or a single dose of 270 μg/kg. In this observational study, there was no stipulated dosing regimen; the choice of dosing and duration of treatment made entirely at the discretion of the prescribing physician. All details of treatments given were collected, and details of bleeds and where they were managed (at home or elsewhere) were recorded.

Participants

Patients were men and boys, aged above 2 years with congenital haemophilia and inhibitors, who were eligible for rFVIIa treatment of haemarthrosis in the elbow, shoulder, wrist, hip, knee, or ankle. Key exclusion criteria included clinically relevant coagulation disorders other than haemophilia A or B and known or suspected allergy to study product. Written informed consent (from the patient or caregiver, as appropriate) was obtained before any study-related activities.

The study was conducted in accordance with Declaration of Helsinki and all its amendments and the Guidelines for Good Pharmacoepidemiology Practice. The protocol was reviewed by the local institutional review boards and/or independent ethics committees. In addition, investigators were required to evaluate the ability of patients (or caregivers) to manage treatment at home, including administration of rFVIIa doses and appropriate assessment of treatment responses.

Assessments and analyses

Data on each joint bleeding episode were collected using patient diaries (Supplementary Table 1, http://links.lww.com/BCF/A25). The main analyses covered the number of bleeds managed partially or completely at home, number of treatments resulting in the control of bleeding episode within 9 h of the first rFVIIa injection, and number of treatments resulting in effective pain relief within 9 h of the first rFVIIa injection. Bleeds were also assessed in target joints, defined as three or more bleeds into the same joint in a consecutive 3-month period [9]. Haemostasis is evaluated by the patient/caregiver as effective (signs/symptoms ceased or decreased substantially), partially effective (signs/symptoms reduced but continued), or ineffective (signs/symptoms the same or worse). Patients with 'effective' or 'partially effective' responses were considered as 'responders'. Pain relief was rated as worse, the same, or better (successful).

Additional analyses included feasibility of home treatment, and treatment convenience and satisfaction. Other evaluations included time between the onset of bleeding and the first injection, time to haemostasis and pain resolution, haemostasis and pain relief at 48 h, total number of injections and doses administered at 48 h, number of re-bleeds (recurrence of bleeding in the same joint within 48 h after complete haemostasis had been achieved), and use of additional medication for haemostasis or pain relief. Endpoints were also evaluated in terms of initial rFVIIa dose, categorized as 120 μg/kg or less, more than 120 to less than 250 μg/kg, or at least 250 μg/kg. Adverse events were recorded throughout the study.

Statistical analysis

The full analysis set (FAS) was defined as all participants who received at least one dose of rFVIIa. Efficacy and patient-reported outcome analyses were based on a modified FAS (mFAS), from which patients in the FAS could be excluded by the investigators for substantial protocol deviation or noncompliance. All endpoints were summarized using descriptive statistics, based on observed data at each visit. Safety analyses included all participants who received at least one dose of rFVIIa.

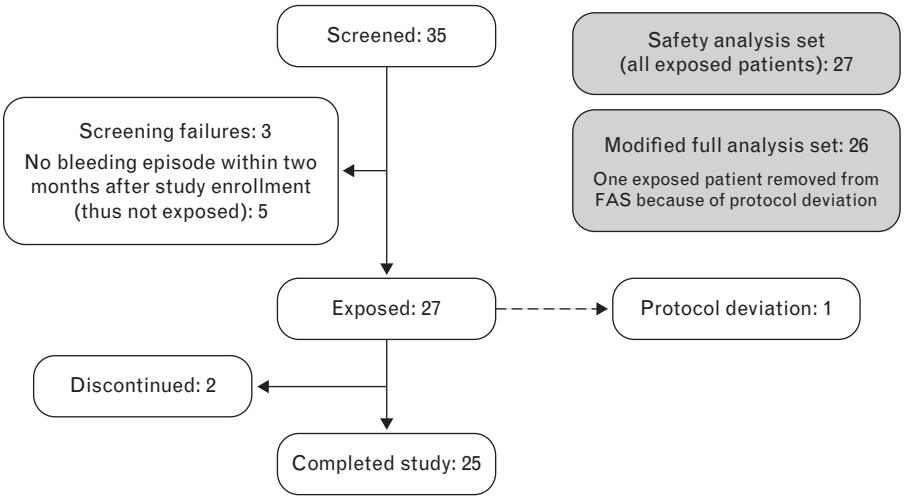
Results

Patient disposition

In total, 35 patients were screened, of whom 27 were enrolled, exposed to study product, and formed the safety analysis set (Fig. 1). One patient was excluded from the FAS as he completed study activities despite having no recorded bleeding episodes during the first 2 months of inclusion in the study; details are shown Supplementary Table 2, http://links.lww.com/BCF/A25. Baseline characteristics of the mFAS are shown in Table 1.

Twenty-five of the 27 enrolled patients (92.6%) completed the study. Two patients discontinued after receiving treatment for some of their bleeding episodes (with discontinuation being initiated by the investigator) as a consequence of noncompliance as judged by the

Fig. 1



Patient disposition.

investigators (i.e. the patient or caregiver not registering the bleeding episodes).

Bleeding episodes

The 26 patients in the mFAS recorded a total of 132 joint bleeding episodes, of which 69 were spontaneous and 62 were traumatic, with one of unknown classification. Seventy-seven bleeds occurred in target joints and 55 in nontarget joints.

Home management

Overall, 84 of 132 bleeding episodes (63.6%) were managed at home (i.e. with treatment partially or completely administered in this setting) (Fig. 2).

Recombinant activated factor VII dosing

The median times from the onset of bleeding to the first injection were 1.5 h for spontaneous bleeds and 2 h for traumatic bleeds. When categorized by dose, 62 bleeding episodes were initially treated with 120 μg/kg rFVIIa or less, 19 with more than 120 to less than 250 μg/kg rFVIIa, and 51 with at least 250 μg/kg rFVIIa. The median (range) cumulative dose within 9 h of first injection was 150.2 (72.7–1334) μg/kg overall, and 145.5 (72.7–1334), 165.1 ($n = 1$) and 225.7 (205.7–245.7) μg/kg in the 120 or less, more than 120 to less than 250 and at least 250 μg/kg groups, respectively. The median cumulative dose within 48 h of first injection was 190.6 (72.7–1525) μg/kg overall, and 180.0 (72.7–1525), 302.3 (165.1–825.7), and 225.7 (91.6–411.4) μg/kg in the three dose groups, respectively, while the median cumulative subsequent dose including treatment beyond 48 h of first injection was 274.8 (72.7–2976) μg/kg overall, and 190.6 (72.7–1525), 302.3 (165.1–825.7), and 458.0 (91.6–2976) μg/kg in the three dose groups.

Table 1 **Baseline characteristics**

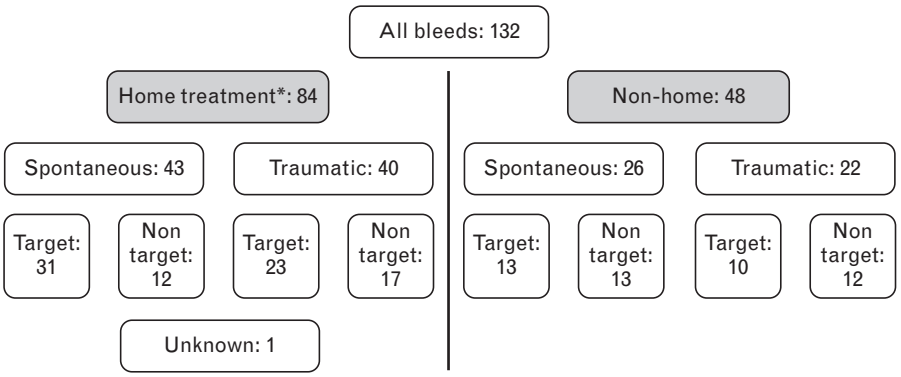
	Full analysis set ($N = 26$)
Age (years)	
Mean ± SD	18.4 ± 8.3
Range	5–41
Ethnicity, *n* (%)	
White	18 (69.2)
Black	2 (7.7)
Other	6 (23.1)
Weight (kg), mean ± SD	51.0 ± 20.4
Height (m), mean ± SD	1.6 ± 0.2
Haemophilia type, *n* (%)	
A	25 (96.2)
B	1 (3.8)
Peak inhibitor titre (BU)	
Mean ± SD	45.5 ± 87.6
≥5 BU, *n* (%)	22 (84.6)
<5 BU, *n* (%)	1 (3.8)
Missing, *n* (%)	3 (11.5)

Haemostasis

Haemostasis data were available for 82 of 84 bleeds managed at home. Successful haemostasis after the first rFVIIa injection was achieved in 72 of 82 (87.8%) bleeding episodes for which data were available at 9 h and 74 of 82 (90.2%) at 48 h (Table 2). When the responder rate for all bleeds was considered, successful haemostasis at 9 and 48 h was achieved in 107 of 124 bleeds (86.3%) and 110 of 124 bleeds (88.7%), respectively. Median time to complete haemostasis was 48 h (range, 1.5–264.0 h) for spontaneous bleeds and 24 h (2.0–324.0 h) for traumatic bleeds.

In target joints, the responder rate for successful haemostasis after 9 h was 45 of 53 (84.9%) for bleeds managed at home compared with 59 of 73 (80.8%) for treatment at all settings. The corresponding figures for nontarget joints

Fig. 2



*Home treatment defined as treatment partially or entirely conducted at home.

Number of bleeding episodes managed at home and not managed at home, categorized as spontaneous and nonspontaneous bleeds, and as affecting target and nontarget joints.

were 27 of 29 (93.1%) and 48 of 51 (94.1%), respectively. Effective haemostasis at 9 and 48 h by initial dose category is illustrated in Fig. 3. The number of injections required until bleed resolution is shown in Fig. 4 for each dose category. Higher initial dosing appeared to be associated with fewer injections.

There were three episodes of re-bleeding (i.e. recurrence of bleeding into the same joint within 48 h of achieving complete haemostasis), two into a target joint, and one into a nontarget joint. Antifibrinolytic treatment was administered in four of 132 (3.0%) bleeds.

Pain relief

Considering bleeds managed at home, pain had improved 9 h after the first rFVIIa injection in 68 of 81 episodes (84.0%), for which data were available, and at 48 h in 71 of 81 bleeds (87.7%). Overall, effective pain relief was reported for 95 of 127 (74.8%) of bleeds at 9 h and 107 of 127 (84.3%) at 48 h. The median time to complete pain relief was 24 h for both traumatic and spontaneous bleeds. Pain relief at 9 and 48 h by initial dose category is shown in Fig. 5.

Considering treatment of target joints, rate of effective pain relief at 9 h for bleeds managed at home compared with those treated at all settings was 42 of 52 (80.8%) versus 51 of 73 (69.9%). The corresponding figures for nontarget joints were 26 of 29 (90%) and 44 of 54 (81%), respectively. Pain medication was used in 46 of 132 (34.8%) instances.

Feasibility of home treatment

Seventy-six of the 84 bleeding episodes managed at home (90.5%) were entirely treated in this setting, with the remaining eight (9.5%) treated partially at home and partially at one or more other locations. Of bleeds entirely treated at home, 67 of 76 (88.2%) required no intervention from a healthcare professional.

Treatment convenience and satisfaction

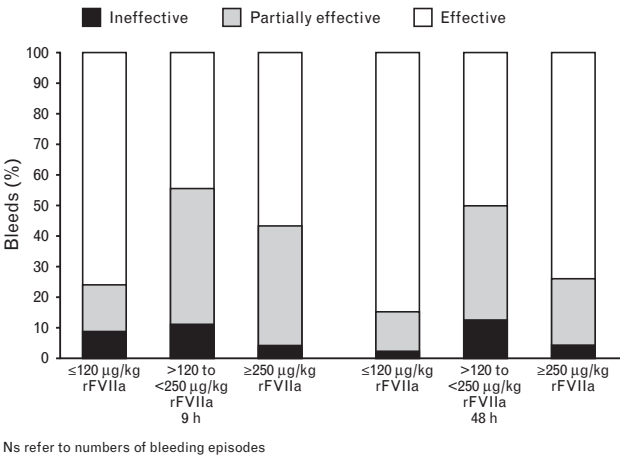
Data on treatment convenience and satisfaction for bleeds at all settings are summarized in Table 3, showing treatment to have been generally well regarded. Traumatic bleeds may, however, require more intensive treatment than spontaneous bleeds. For example, while patients (and/or their caregivers) reported interruption to their daily activities as a result of spontaneous bleeds in 19 instances, [mean duration of interruption, 65.5 ± 51.3 h (median, 49.0 h)], for traumatic bleeds there were 30 such reports [mean duration of interruption, 121.1 ± 161.5 h (median, 73.5 h)]. Also, in five instances, patients with spontaneous bleeds were hospitalized for a median

Table 2 Assessment of haemostasis

	Bleeds managed at home[a]		All bleeds	
Evaluation	9 h	48 h	9 h	48 h
Responder rate for successful haemostasis[b], *n*/*N* (%)	72/82 (87.8)	74/82 (90.2)	107/124 (86.3)	110/124 (88.7)
Effective treatment, *n*/*N* (%)	52/82 (63.4)	60/82 (73.2)	68/124 (54.8)	80/124 (64.5)
Partially effective treatment, *n*/*N* (%)	20/82 (24.4)	14/82 (17.1)	39/124 (31.5)	30/124 (24.2)
Ineffective, *n*/*N* (%)	6/82 (7.3)	3/82 (3.7)	13/124 (10.5)	6/124 (4.8)
Missing, *n*/*N* (%)	4/82 (4.9)	4/82 (4.9)	4/124 (3.2)	8/124 (6.5)

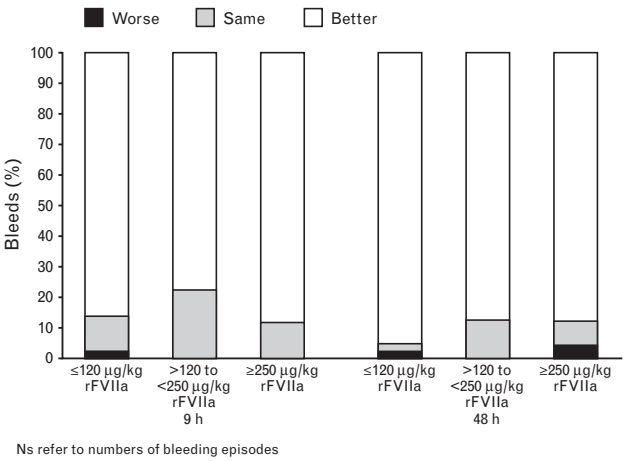
[a] Treatment partially or completely administered at home. [b] Overall response rate, determined according to patient/caregiver ratings of 'Effective' (signs/symptoms ceased or decreased substantially decreased) and 'Partially effective' (signs/symptoms reduced but continued).

Fig. 3



Efficacy of haemostasis at 9 and 48 h after receiving the first injection of rFVIIa, by initial rFVIIa dose category. Haemostasis was categorized by the patient or caregiver as effective (signs/symptoms ceased or decreased substantially), partially effective (signs/symptoms reduced but continued), or ineffective (signs/symptoms the same or worse).

Fig. 5



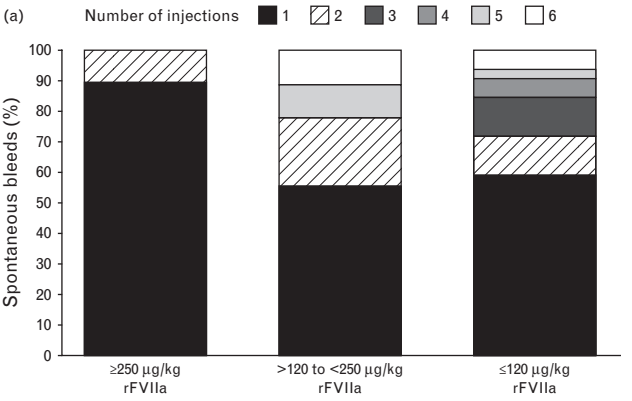
Change in pain intensity within 9 and 48 h of receiving the first injection of rFVIIa, categorized according to initial rFVIIa dose category. The change in pain intensity was categorized by the patient or caregiver as worse, the same, or better than baseline.

duration of 2.0 days, while in 10 instances, patients with traumatic bleeds were hospitalized for a median duration of 4.0 days. The median (range) number of injections required until bleed resolution was 1.0 in the at least 250 μg/kg (range, 1.0–14.0) and more than 120 to less than 250 μg/kg dose groups, and 2.0 in the 120 μg/kg dose or less group.

Safety

One adverse event was reported during the study (acute tonsillitis), which was not considered to be related to study treatment. No deaths, serious adverse events, or events of medical interest occurred during the study, and no patient withdrew because of adverse events.

Fig. 4



Number of rFVIIa injections required until bleed resolution, categorized according to initial rFVIIa dose category, for (a) spontaneous bleeds and (b) traumatic bleeds.

Discussion

Inhibitors are a major complication in patients with haemophilia, and efficient treatment must be administered as early as possible. rFVIIa is an effective and convenient treatment for haemophilia with inhibitors [5,10]. Notably, real-world data show that early rFVIIa treatment – typically linked with home treatment – is associated with a lower incidence of re-bleeding and an overall decreased consumption of haemostatic product [11]. In the present study, haemostatic response and pain relief at 9 and 48 h after bleed onset were numerically

Table 3 Treatment convenience and satisfaction

Parameters relating to convenience	
Interruption of patients'/caregivers' daily activities, mean ± SD hours	99.6 ± 132.3 (49 bleeds)
Number of injections per bleed until bleed resolution, median (range)	1.0 (1.0–14.0)
Number (%) of joint bleeds that required hospitalization, emergency room visit or unscheduled treatment centre visit	55 (42.0)
Satisfaction: voluntary questions evaluating 129 bleeding episodes	
Bleeding episodes for which respondents were 'satisfied' or 'very satisfied' with the way in which treatment relieved bleed symptoms, *n*, (%)	115 (89.1)
Bleeding episodes for which respondents were 'satisfied' or 'very satisfied' with the time taken for treatment to start working, *n* (%)	106 (82.2)
Bleeding episodes for which respondents considered it 'easy' or 'very easy' to use rFVIIa to treat a bleed, *n* (%)	123 (95.3)
Bleeding episodes for which respondents considered rFVIIa to be 'effective' or 'partially effective', *n* (%)	124 (96.1)

better for bleeds treated at home compared with those treated at all settings. Consistent with earlier studies, higher initial dosing was associated with fewer injections to achieve bleed resolution, with most patients receiving higher rFVIIa doses requiring only a single injection [11,12]. Even in the 120 μg/kg or less group, however, some patients required only a single dose of rFVIIa to achieve bleed resolution. This is consistent with a previous study showing that 29% of patients with mild-to-moderate bleeds required only one injection of 90 μg/kg rFVIIa to achieve initial haemostasis [8]. Assessment of convenience and satisfaction in the present study showed that bleeding episodes place a considerable burden on patients and caregivers and that satisfaction with treatment is high.

The feasibility and effectiveness of home treatment with rFVIIa in this study involving developing countries are consistent with earlier studies conducted in developed countries [6–8], such as a pilot study conducted in 10 Italian patients with inhibitors (53 bleeding episodes) who self-administered rFVIIa [6]. Successful haemostasis was achieved in 90% of bleeds. Notably, effective haemostasis was significantly associated with earlier intervention compared with partially effective or ineffective treatment (median time between bleeding onset and first injection: 0.6 and 2.7 h, respectively; $P = 0.02$). A US open-label study of home treatment with rFVIIa found that haemostasis was effective in 92% of bleeds after a mean of 2.2 injections [8]. More recently, a registry study evaluated home treatment in 85 patients (494 bleeding episodes) [7]. For spontaneous bleeds, successful haemostasis at 9 h was achieved for 85% of bleeds treated with 120 μg/kg or less rFVIIa, 96% with more than 120 to less than 250 μg/kg rFVIIa, and 86% with at least 250 μg/kg rFVIIa. As in the present study, higher initial dosing was associated with fewer injections. In the Haemophilia and Thrombosis Research Society registry (129 patients reporting 2041 bleeds), most bleeds were treated at home [13,14]. Overall efficacy (cessation of bleeding within 48 h) ranged from 89% in spontaneous bleeds to 93% in traumatic bleeds, and most bleeds were treated with a median of 3–4 injections [13]. In patients who received higher initial doses of rFVIIa, effective haemostasis was achieved in 93% of bleeds overall [14].

An important advantage of home treatment is that it allows rapid initiation of treatment after the onset of bleeding, which may be a particular issue in developing countries with limited access to treatment centres. Rapid control of bleeding episodes is particularly important for patients with inhibitors as it can increase the chances of successful haemostasis [6,8,12], which may in turn minimize joint damage and improve quality of life.

The present study was strictly observational, with a heterogeneous patient population with regard to demographics, treatment regimens, and disease management practices. Furthermore, the study was not powered to compare the outcomes of treating spontaneous and traumatic bleeding episodes, nor to compare the outcomes of different initial dosing or target versus nontarget joints. Validated scales were not used for the evaluation of pain relief, as such scales are not commonly used in the countries where this study was performed. Their use would, therefore, be inappropriate for an observational study. Despite these limitations, the study provides valuable data on the feasibility of home treatment in developing countries, adding to the body of evidence already available from the developed world.

In conclusion, our results support data from comparable studies showing similar overall effectiveness and safety of rFVIIa across a range of initial dosing patterns. Use of higher initial doses was, however, associated with a lower number of total injections. Treatment satisfaction was high. Home treatment with rFVIIa is, therefore, effective, convenient, and feasible in developing countries, with no associated safety concerns. These results will help to increase awareness and aggregate experience, fostering confidence in home management of haemophilia patients with inhibitors in developing countries. In addition, the study results reflect the need in developing countries for the application of comprehensive home-treatment programmes with a systematic and comprehensive patient/caregiver educational approach. This would encourage better adherence with home treatment in general and with 'complete' home treatment for mild-to-moderate bleeding episodes unless otherwise recommended for individual cases. Optimal dosing choices for home treatment should consider the site, severity, cause, and type of bleeding, with appropriate follow-up by the treating centres.

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Conflicts of interest

There are no conflicts of interest.

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