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Management of intracranial surgery for refractory epilepsy in severe factor VII deficiency: choosing the optimal dosing regimen

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Inherited factor VII deficiency (FVIID) is the most common 'rare' bleeding disorder and is characterized by a variable bleeding tendency. A subgroup of patients with FVIID present with a severe clinical bleeding phenotype characterized by spontaneous bleeding in early infancy [1]. Surgery in such patients carries a risk of bleeding and the optimal treatment regimen for major surgeries has still not been defined. Continuous infusion of rFVIIa (CI-rFVIIa) has been used most commonly during orthopaedic surgery with good outcomes; however, experience with CI-rFVIIa is limited, with very few data on comparisons between bolus and continuous infusion regimens [2].

We present a patient with severe FVIID (FVII activity < 1 IU mL^{-1}) with intractable atonic (drop) seizures attributed to a spontaneous intracranial haemorrhage (ICH) in the neonatal period who underwent a total corpus callosotomy for control of seizures. Preoperatively, we administered rFVIIa in three dosing regimens so as to enable us to choose the optimal regimen for use during and after his planned major neurosurgical procedure. Preoperatively, we monitored tissue factor thromboelastographic (TF-TEG) parameters, prothrombin time (PT) and FVII activity after the three rFVIIa doses. Eventually, we chose one dosing regimen for use during surgery and the patient successfully underwent the surgery with no bleeding complications and had an excellent outcome.

The patient is an 8-year-old male of Middle Eastern origin who was diagnosed with severe FVIID in the neonatal period. He developed a right-hemispheric ICH at 24 days of age. At approximately seven and a half years of age, he developed recurrent seizures consisting of sudden drops that were precipitated by unanticipated auditory stimuli. These gradually increased in frequency from 2 per day to 20 per day and the seizures were resistant to different antiepileptic medications. Due to the seizures, the patient sustained multiple falls and developed recurrent musculo-skeletal bleeding episodes. Due to the risk for secondary haemorrhage as well as the negative impact on his quality of life, surgical options were explored. Vagal nerve stimulation (VNS), corpus callosotomy or a right hemispherectomy was considered for controlling his seizures. The major disadvantage of hemispherectomy was potential catastrophic bleeding while that of VNS was that rarely does this abolish all seizure episodes. A more conservative surgery (i.e. total corpus callosotomy) was considered to be the most reasonable option, offering an 80% chance of total seizure control in atonic (drop) seizures.

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Preoperatively, the patient electively received three different dosing treatments with rFVIIa (NovoSeven® RT; Novo Nordisk A/S, Bagsvaerd, Denmark) on three separate days: (i) 1 mg bolus (27 μg kg^{-1}, low-dose bolus, LDB-rFVIIa), (ii) 2 mg bolus (54 μg kg^{-1}, high-dose bolus, HDB-rFVIIa) and (iii) continuous infusion rFVIIa (CI-rFVIIa). Continuous infusion dose was administered as follows. The patient received a bolus of 0.3 mg (8 μg kg^{-1}) followed by a continuous infusion of 1.7 mg over the next 5 h (~9 μg kg^{-1} h^{-1}). Due to the small volume of reconstituted rFVIIa, 1.7 mg of rFVIIa was diluted in 15 mL of normal saline and infused at 3 mL h^{-1}.

As he was on secondary prophylaxis with rFVIIa, the prophylactic dose was held on the day of testing to allow for a washout interval of at least 24 h. The rFVIIa was infused via a tunnelled central venous catheter and all samples were collected via a peripheral venous draw. Samples were collected for PT, FVII activity and TF-TEG at baseline (pre-rFVIIa) and at 1, 2, 4 and 6 h after the bolus doses. For CI-rFVIIa, samples were drawn at baseline and at 15 min and at 1, 2 and 4 h. Factor VII activity was tested in citrated plasma (3.2%) using a one-stage mechanical clotting assay on the STA-R Evolution (Diagnostica Stago, Parsippany, NJ, USA). The assay utilized a calcium thromboplastin from rabbit cerebral tissues (Neoplastine CI; Diagnostica Stago) with human factor VII-deficient plasma (George King Bio-Medical, Inc. Overland Park, KS, USA) to measure the clotting time vs. the standard plasma (STA Unicalibrator; Diagnostica Stago). TF-TEG was performed as per a published method [3]. The results are documented in Table 1 and Fig. 1.

As the PT, FVII and TEG parameters were most stable after CI- rFVIIa, a decision was made to use this regimen for surgery. The patient received CI-rFVIIa as described above (the bolus dose was given just prior to surgery followed by continuous infusion during and after surgery). The patient underwent the surgery with an estimated blood loss of 50 mL. We were able to decrease his CI-rFVIIa further on postoperative days 2 (7 μg k^{-1} h^{-1}) and 3 (4.5 μg k^{-1} h^{-1}) as his PT, FVII activity and TF-TEG were in the acceptable range with no bleeding (Table 2). The continuous infusion was stopped on postoperative day 8 and the patient was discharged home on prophylactic rFVIIa regimen (home regimen). The patient has been seizure free for more than 9 months after surgery and continues on secondary rFVIIa prophylaxis (2 mg rFVIIa every other day) for prevention of recurrent ICH.

Congenital severe FVII deficiency (FVIID) is a rare bleeding disorder characterized by broad clinical heterogeneity. Replacement of FVII by giving plasma-derived FVII, rFVIIa, fresh frozen plasma or prothrombin complexes remains the treatment of

Table 1. Laboratory data after preoperative test doses of rFVIIa.

	Dose	PT pre (s)	PT immediate post (s)	FVII act immediate post (%)	PT 1 h (s)	FVII act 1 h (%)	PT 2 h (s)	FVII act 2 h (%)	PT 4 h (s)	FVII act 4 h	PT 6 h (s)	FVII act 6 h (%)	R on TF-TEG
Low-dose bolus	1 mg	74.9	Not done	Not done	9.2	479	10.4	180	12.3	70	14	34	Short R time
High-dose bolus	2 mg	54.9	Not done	Not done	Sample clotted	534	10.8	Sample clotted	10	242	12	79	Extremely short R time
Continuous infusion	Bolus of 0.3 mg and then 1.7 mg over 6 h (8 μg kg^{-1} followed by a continuous infusion	31.2	9.2	441	9.2	441	9.2	470	9.1	493	(not done)	(not done)	Short R time on TEG

rFVIIa, recombinant factor VIIa; act, activity; TF-TEG, tissue factor thromboelastography.

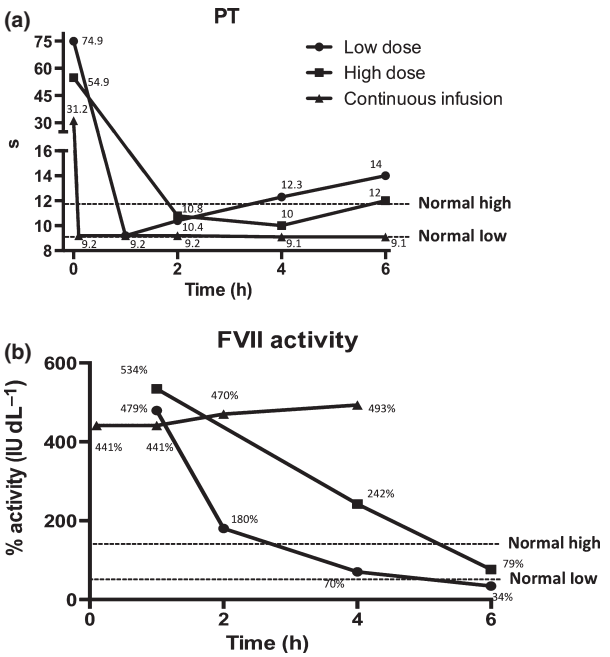

Fig. 1. Sequential changes in prothrombin time (PT) and factor VII activity (refer Table 1 for actual numbers).

choice for patients with bleeding and for those undergoing surgery [4]. Bleeding from surgical procedures has been reported in one-third of the patients with FVIID and risk of bleeding varies with the type of surgery, tissue or organ involvement and the type of anaesthesia [5]. Previous reports of bolus doses ranging from 15 to 90 μg kg^{-1} have been used in patients at an interval of 4–6 h [6]. Such regimens, however, lead to wide fluctuations in the FVIIa activity with supratherapeutic levels after the bolus doses and sub-therapeutic levels by hour 4 [7]. Factor VII replacement after surgery has also been associated with the development of an inhibitor and thrombotic complications [4,8].

Recently, an analysis from the Seven Treatment Evaluation Registry for surgical procedures was published in which surgeries were classified as either major (open abdominal, orthopaedic, cardiovascular or neurosurgery) or minor [5]. Of the 41 elective surgeries in 34 patients, only three patients received continuous infusions. There were seven patients with FVII level of <1% but none had central nervous system bleeding and presumably did not undergo a neurosurgical procedure. The minimally effective dose was deemed to be 13 μg kg^{-1} body weight with two additional doses. This supports the concept proposed by other researchers that in FVIID patients, a lower dose of FVIIa may be needed for achieving haemostasis [9]. Given the wide fluctuations in FVII levels obtained with bolus dosing and the risk of inhibitor formation or thrombosis with such dosing regimens, we felt that low-dose CI rFVII was the optimal regimen for our patient.

There is no consensus regarding the dose or rate of continuous infusion of rFVIIa. Schulman *et al.* reported bolus doses in their study ranging from 4 to 66 μg kg^{-1} followed by continuous infusion with variable doses [6]. A publication by Tran *et al.* reported the effective use of CI-rFVIIa in 13 major surgeries out of 25 surgical procedures, all of which were non-central nervous system surgeries [2]. They used a bolus dose of 8.5 μg kg^{-1} followed by a rate of 0.9 μg kg^{-1} h^{-1} along with tranexamic acid and reported a significant reduction in use of medication usage and cost.

In our patient, we were able to compare three dosing regimens prior to a major elective neurosurgical procedure. After LD-bolus dose, the PT was found to be prolonged after 4 h. Conversely, several of the samples after HDB-rFVIIa were clotted, suggesting extremely high levels of FVII. An analysis of laboratory measurements (PT, FVII levels and TEG), revealed low dose continuous infusion to be superior to bolus doses. This regimen was subsequently chosen for the surgery. Due to a possible additional risk of thrombosis with tranexamic acid, we chose to eliminate the use of tranexamic acid (as described previously by Tran *et al.*) but chose to give a higher dose of continuous infusion of rFVIIa [2]. Once surgical haemostasis was achieved, we were able to rapidly wean the CI-rFVIIa dose on days 2 and 3 postoperatively with normalization of haemostatic parameters.

To our knowledge, this is the first study that has compared three different dosing regimens prior to an elective major neurosurgical procedure. We found that

Table 2. Intra- and postoperative management of continuous infusion of rFVIIa.

	Preoperative	Intraoperative	Postoperative day 1	Postoperative day 2	Postoperative days 3–7
Bolus dose	0.3 mg (8 μg kg^{-1})	NA	NA	NA	NA
Continuous infusion (μg kg^{-1})	1.7 mg/5 h (9 μg kg^{-1} h^{-1})	2 mg/6 h (9 μg kg^{-1} h^{-1})	2 mg/6h (9 μg kg^{-1} h^{-1})	2 mg/8 h (7 μg kg^{-1} h^{-1})	2 mg/12 h (4.5 μg kg^{-1} h^{-1})
PT	Not done as baseline levels available from preoperative testing (Table 1)	9.4 s	9.1 s	10 s	9.4–9.9 s
FVII activity	Not done as baseline levels available from preoperative testing (Table 1)	361%	361%	291%	285–311%
R time TF-TEG	Not done as baseline levels available from before	Short R time	Short R time	Short R time	Normal R time
Outcomes and interventions	Start CI-rFVIIa	Continue CI-rFVIIa; no bleeding	Decrease CI-rFVIIa; no bleeding	Decrease CI-rFVIIa; no bleeding	Continue CI-rFVIIa; no bleeding

PT, prothrombin time; CI, continuous infusion; rFVIIa, recombinant factor VIIa.

continuous infusion rFVIIa was superior to bolus rVIIa regimens in terms of better maintenance of steady coagulation parameters and cost-effectiveness. Low-dose continuous infusion rFVIIa may be the optimal way to manage surgical procedures, especially major procedures in patients with severe FVIID.

Author contribution

MR was responsible for the overall conduct of this study; MR, KS, HC, SS mutually decided the regimen for use during surgery; SS performed the surgery; MF helped coordinate the study; MC managed the actual perioperative regimen; All authors contributed to manuscript writing, editing and reviewed the final submission.

Disclosures

M Rajpurkar has received honoraria from Novo Nordisk for consultation. MJ Frey is a speaker for Bayer and Nursing Advisory Board for Novo Nordisk, Baxter, Biogen Idec and Kedrion. M Callagahan, K Set, H Chugani, S Sood stated that they had no interests which might be perceived as posing a conflict or bias.

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High titre inhibitor to factor VIII in a haemophilia carrier

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Several aspects of mild haemophilia, defined as factor VIII coagulant activity (FVIII:C) between 0.05 and 0.40 IU mL^{-1}, are currently under investigation. One is inhibitor development and treatment. Patients with mild haemophilia have been recognized as a low-risk group, with an overall incidence estimated between 3% and 13%. Despite the lower risk of appearance compared with severe haemophilia, inhibitor can be an important clinical challenge regarding management of bleeding and eradication. It has been demonstrated that an intensive exposure to FVIII, mainly in a surgical setting, predisposes to inhibitor appearance, the risk being higher in carriers of the Arg593Cys missense mutation in the F8 gene. This mutation, for instance, modifies FVIII three-dimensional structure since cysteine is ought to form disulphide bridges [1].

In haemophilia carriers, one of the two X-chromosomes is inactivated during embryonic life [2]. Indeed FVIII levels may range widely because lyonization is not always random. Abnormalities in the initial choice of X-chromosome inactivation have been reported in haemophilia carriers with bleeding symptoms and FVIII levels far below 0.50 IU mL^{-1} [3]. Carriers with low FVIII levels can bleed resembling the clinical picture of mild haemophilia [4]. Bleeding haemophilia carriers sometimes need replacement therapy, typically in major surgical procedures where desmopressin may not ensure sufficiently prolonged high levels of FVIII. To the best of our knowledge, only one case of spontaneous inhibitor occurrence has been reported so far in a female carrier of haemophilia [5].

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