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Recombinant, activated factor VII for surgery in factor VII deficiency: a prospective evaluation – the surgical STER

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Summary

Excessive bleeding represents a major complication of surgical interventions and its control is especially relevant in patients with Congenital Bleeding Disorders (CBD). In factor VII (FVII) deficiency, scanty data on surgery is available to guide treatment strategies. The STER (Seven Treatment Evaluation Registry) is a multi-centre, prospective, observational, web-based study protocol providing the frame for a structured and detailed data collection. Inhibitor occurrence was checked in a centralized fashion. Forty-one surgical operations (24 'major' and 17 'minor') were performed in 34 subjects with a carefully characterized FVII deficiency under the coverage of recombinant activated Factor VII (rFVIIa). Bleeding occurred during three major interventions of orthopaedic surgery, but rFVIIa was given at very low dose in each case. An antibody to FVII was observed in one patient who underwent a multiple dental extraction. No thromboses were reported during the 30-d follow up period. Replacement therapy with rFVIIa proved effective when suitable doses were used, which, during the period of maximum bleeding risk (the day of operation), were calculated (Receiver Operated Characteristic analysis) to be of at least 13 μg/kg/body weight per single dose and no less than three administrations. This indication is important especially in the case of major surgery.

Keywords: surgery, replacement therapy, factor VII deficiency.

Bleeding during and after surgery is a potential complication for any surgical intervention and a major concern for the surgeon, so its control is essential for the successful outcome of surgery. This aspect is highly relevant for patients with a Congenital Bleeding Disorder (CBD) as surgical interventions require a multidisciplinary approach with the involvement of the haematologist in order to set up a strategy for the prevention of this potentially severe complication. The mainstay for bleeding prevention is Replacement Therapy (RT) based on the substitution of the missing factor, in order to correct the clotting defect.

As the patient with CBD is at risk of bleeding for several days, bleeding prevention requires the administration of the missing factor at dosages higher than those currently used, over a fairly short period of time. This may induce higher than normal levels, which may facilitate the occurrence of side effects triggered by RT and/or the surgical procedure and anaesthesia.

Factor VII (FVII) deficiency is a CBD with an estimated prevalence of 1/500 000 individuals (Mannucci *et al*, 2004) without ethnic or gender predilection (Perry, 2002; Mariani *et al* 2005, Roberts & Escobar, 2006; Herrmann Wulff *et al*, 2009. Treatment demands vary considerably amongst FVII-deficient patients, ranging from none or rare on-demand treatment to frequent factor administration required for long-term or short-term prophylaxis, such as for major surgical

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interventions (Mariani *et al* 2003, 2005; Mariani & Dolce, 2005; Herrmann Wulff *et al*, 2009). The variability of RT requirement depends, in part, on the clinical and clotting severity of the defect, but in surgery other elements should be taken into account for the assessment of bleeding risk, such as type of surgery, tissue/organ involved, and type of anaesthesia. Further, bleeding can hardly be foreseen in this CBD and even very low FVII activity levels may fail to predict surgical bleeding.

In general, surgical bleeding is not an infrequent symptom in FVII deficiency, reported in about 1/3 of the cases (Mariani & Dolce, 2005; Mariani *et al*, 2005). A recent review on the management of FVII deficiency with rFVIIa (activated FVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) found no consistently effective nor dose schedules in the analysis of both the compassionate study and in independent studies with reference to surgery (Mariani *et al*, 2006).

As FVII deficiency is a rare bleeding disorder, a limited number of patients are available for follow up in most treatment centres. For this reason interventional studies would face, in this particular study population, recruitment problems. The STER (Seven Treatment Evaluation Registry) is intended to elucidate treatment modalities in a well defined collective of FVII deficient patients, carefully characterized concerning their clinical and clotting phenotypes. Keeping in mind that treatment decisions are made with more emphasis on personal clinical experience than on consolidated clinical evidence, the general purpose of the STER is to document treatment practices for spontaneous bleeds, surgery, prophylaxis and related side effects. In the present study, our attention focused on the evaluation of a considerable number and variety of surgical cases treated with rFVIIa.

Materials, methods and patients

The STER is a multi-centre, prospective, observational, web-based registry created to collect and describe treatment modalities and outcomes in congenital FVII deficiency. The study protocol has been created following strictly controlled data collection procedures set up by the International FVII Deficiency Study Group (IF7SG) and based on experience gained from previous studies (Mariani *et al* 2003, 2005, Mariani *et al*, 2006; Bernardi *et al*, 2009; Ingerslev *et al* 2005). Data collected online are stored in a custom designed database. The STER system is a web application developed in NET. Data is stored in a Microsoft SQL Server 2000 database, which contains the electronic Case Report Form pages with no components installed on the centre computers. The investigator accesses the system when a patient needs a treatment for: (i) Spontaneous bleeding episodes, (ii) Prophylaxis courses and (iii) Surgical interventions. For the latter, key assessments of the study protocol are designed to capture the following items: (i) indication for surgery and date of the intervention, (ii) description of surgery, (iii) detailed daily recording of substitution therapy, (iv) recording of concomitant medications (i.e. antifibrinolytic drugs used prior, during and after, heparin or other thrombo-prophylactic agents), (v) recording of concomitant illness, (vi) recording of critical surgery results and outcome, (vii) recording the adverse events (anaphylactoid reactions, thrombotic events, disseminated intravascular coagulation reactions, bleeding and mortality).

In order to evaluate subjects bearing a clear risk of surgical bleeding, patients with FVII coagulant activity (FVII:C) levels ≤20% of normal and/or a mutation known to be associated with a significant FVII deficiency, disregarding gender and age, have been enrolled in the registry. Enrolment occurred only if and when the treating physician deemed that a RT was necessary to prevent bleeding during a surgical procedure. FVII:C was assayed at each participating centre laboratory using high-sensitivity thromboplastins [International Sensitivity Index (ISI) close to 1]. Patients were also carefully characterized with respect to their bleeding phenotype by recording the number and the kind of the different symptoms reported. Concerning RT data, the following parameters were evaluated: (i) RT duration (d), (ii) total number of RT injections, (iii) number of injections per day, (iv) total RT dose, (v) mean daily dose (total dose/number of treatment days), (vi) mean single dose (total dose/number of injections) and (vii) first dose and total dose on day one (day of the operation).

Evaluation by the treating physician and/or the amount of blood loss during the intervention as well as the number of RBC units given was taken into account when assessing a bleed. Thrombosis (venous or arterial) diagnosis was based on clinical suspicion and confirmed by imaging. The screening for inhibitory antibodies to FVII was carried out in a centralized fashion (University Hospital Aarhus/Skejby, Denmark) by a standard assay and 30-d plasma samples were analysed. The method used is a modification of the Bethesda assay, sensitive to 0·45 Bethesda units (BU)/ml of inhibitor, where 1 U is the antibody amount capable of reducing FVII by 50% after 2 h of incubation (Ingerslev *et al* 2005).

Surgical interventions were categorized as suggested by Kitchens (2002); briefly, *major surgery* included 'invasive procedures such as open abdominal or orthopaedic surgery' and 'cardiovascular and neurological surgery', whereas *minor surgical procedures* included 'endoscopy with biopsies, arthroscopic surgery, lymph node biopsies, skin or breast biopsies, and complicated dental work'.

New records were periodically reviewed by an adjudication committee (GM, AD and an expert from the Central Records Office) and the investigators were asked to complete the file blanks before definitive approval.

The research proposed by the STER Study Group was approved by the Ethics Committee of L'Aquila University (coordinator's institution) and, in parallel, by the Committees of the other institutions involved. The STER protocol is publicly available at http://www.targetseven.org.

Statistical analysis: Statistical analysis was based on descriptive measures of the distribution, such as mean for the position

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parameter and range for the variability. To evaluate which RT doses/schedules could ensure haemostasis in the surgical setting on the basis of our data, the Receiver Operating Characteristic (ROC) analysis was performed for the first dose, the total dose given on the day of operation and for the total number of doses, providing the Area Under the Curve (AUC) values and the corresponding cut-off values. For safety purposes, a sensitivity at 100% level (probability that a result will be positive even if a complication occurs) was chosen. Where useful, the Confidence Interval (CI) of the test value and the *P*-value (*P*; considered significant when <0·05) were provided. Analyses were carried out using the medcalc® software version 7.4.1.2 (Mariakerke, Belgium) (http://www.medcalc.be).

Results

As of November 2009, 41 elective surgical interventions (performed by nine haemophilia treatment centres in five countries), were carried out in FVII-deficient subjects under the coverage of NovoSeven®. The 41 surgeries were performed in 34 patients (18 females, 16 males) with residual FVII:C levels between <1% and 20% (Tables I and II). Seven patients underwent two different surgeries. Twenty-one out of 34 of the patients (61·7%), were previously symptomatic. There was no age difference ($P = 0·5$) between symptomatic (44 years, range 1–78) and asymptomatic (40 years, range 2–75) individuals. Detailed clinical and clotting phenotypes of the patients are shown in Table II. There were more previously symptomatic females than males (72·2 vs. 50·0%) (Tables I and II).

In order to provide information useful to the treating physician, the interventions described were divided into Major (Table III) and Minor (Table IV) (Kitchens, 2002) and allocated to the following categories: (i) Orthopaedic surgery ($n = 6$), (ii) Neuro-, Head & Neck-, Eye- and ear, nose and throat (ENT)-surgery ($n = 7$), (iii) Abdominal and Obsterical & Gynaecological surgery ($n = 10$), (iv) Dental extractions ($n = 10$), (v) Other minor surgical interventions and invasive procedures ($n = 7$), (vi) Cardiovascular surgery ($n = 1$).

NovoSeven® was given by bolus in 38 instances and by continuous infusion in only three patients (Tables III and IV). Bleeding was reported during three surgical interventions of orthopaedic surgery (Table III); the amount of blood lost was 1800, 1700 and 500 ml, respectively, and RBC units were transfused following the first two operations. The main features regarding RT are provided in Table V.

No thrombosis episodes were reported during the 30-d surgical follow up. An inhibitor to FVII was found 30 d after a minor surgical procedure (Table IV); the patient had a complex RT history and had previously received different products. The maximum titre was 18 BU.

Given that bleeding complications occurred only on the first treatment day (the day of maximum bleeding risk), we focused our attention on this, in order to detect the minimal advisable RT amount to administer. Independently of the FVII:C baseline levels and considering a sensitivity of 100%, ROC analysis identified a first dose value of 13 μg/kg (AUC = 0·87, CI 0·72–0·95, $P = 0·0005$) (Fig. 1) with no <three doses (AUC = 0·8, CI 0·67–0·9, $P = 0·05$). Total dose on the first day did not appear to be a parameter related to the risk of bleeding (AUC 0·59, $P = 0·58$).

Discussion

The structure of our study protocol provides the framework for a standardized and systematic evaluation of complex case reports. Within the field of surgery, this endeavour is particularly complex as RT is often long lasting and variable in terms of doses and schedules, factors that highlight the value of surgery for the evaluation of treatment effectiveness and adverse events. Our report comprises only interventions carried out with NovoSeven®, a treatment becoming the most used in FVII deficiency, worldwide.

There are no substantial demographic and clinical differences between this cohort and that of the previously published IF7 cohort (Mariani *et al* 2005, Bernardi *et al*, 2009), in terms of prevalence of symptoms and of severity spectrum of the disease (Table II). The only difference is the presence of only females in the lowest FVII:C level group. At any rate, in previous studies (Mariani *et al* 2003, 2005, Bernardi *et al*, 2009), we consistently reported the lack of difference between genders in relation to clinical severity. Therefore, it appears

Table I. Patients demographic and general features.

	All		Males		Females	
	n (%)	Previously symptomatic (%)	*n* (%)	Previously symptomatic (%)	*n* (%)	Previously symptomatic (%)
All	34	21 (61·7)	16 (47·1)	8 (50)	18 (52·9)	13 (72·2)
FVII:C levels (%)						
≤1	7 (20·6)	6 (85·7)	0 (0)	0 (0)	7 (38·8)	6 (85·7)
>1–10	15 (44·1)	10 (66·6)	9 (56·3)	6 (66·6)	6 (33·4)	4 (66·6)
>10–20	12 (35·3)	5 (41·6)	7 (43·7)	2 (28·6)	5 (27·8)	3 (60)
Median age (range)	46 years (0·6–79)		47 years (2–75)		38 years (0·6–79)	

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Table II. Clinical picture of the patients.

Patient	Gender	Age (years)	FVII activity (%)	Number of recorded symptoms	Type of recorded symptoms
1	Female	66	<1	7	Br, Ep, Gu, He, Pe Me, Sc
2	Female	36	<1	6	Br, Ep, Gu, Pe, Me, Sc.
3	Female	53	<1	6	Br, Ep, Gu, Pe, Gi, Me
4	Female	59	<1	5	Br, Ep, Gu, Me, Mu
5	Female	23	<1	1	Me
6	Male	59	1	6	Ep, Gi, Gu, Hr, Mu, Sc
7	Female	11	1	5	Br, Ep, Gu, Hr, Sc
8	Female	76	1	0	*asymptomatic*
9	Male	2	1	0	*asymptomatic*
10	Male	68	1·7	4	Br, Ep, Gi, Gu
11	Male	65	1·9	1	Gi
12	Male	62	2	4	Ep, Gu, Hr, He
13	Male	42	3	1	Su
14	Male	5	3	0	*asymptomatic*
15	Female	69	4	4	Br, Ep, Gu, Me
16	Male	53	5	0	*asymptomatic*
17	Female	79	6	4	Br, Ep, Hr, Su
18	Male	46	8	1	Gi
19	Female	33	8	0	*asymptomatic*
20	Female	21	9	1	Me
21	Female	0·6	10	1	Gi
22	Female	66	10	0	*asymptomatic*
23	Male	47	11	0	*asymptomatic*
24	Male	49	12	0	*asymptomatic*
25	Male	8	12	0	*asymptomatic*
26	Female	8	13	1	Su
27	Female	28	13	0	*asymptomatic*
28	Female	55	15	1	Mu
29	Male	39	15	1	Ep
30	Male	16	17	0	*asymptomatic*
31	Female	40	18·6	0	*asymptomatic*
32	Male	75	19	0	*asymptomatic*
33	Male	20	20	2	Ep, Su
34	Female	35	20	1	Me, Ep

Bleeding symptom legend: Ep, epistaxis; Su, surgical; Br, bruising; Gu, gum; Pe, peritoneal haemorrhage; Me, menorrhagia; Sc, subcutaneous; Gi, gastrointestinal; Mu, muscle; He, haematuria; Hr, haemarthrosis.

that no relevant selection biases affecting the treatment evaluation were identified.

Efficacy evaluation showed that bleeding occurred in 3/41 reports (two patients), all of which concerned major surgical orthopaedic procedures. Worth noting, two bleeding episodes were reported in the same, severely deficient (FVII:C <1%), previously symptomatic patient. They occurred during two major procedures: a total knee replacement and a total hip replacement, 1 year apart (Table III). The third orthopaedic surgery-related bleed occurred in a mild FVII deficient patient with a positive history for bleeding. These three events had in common the fact that haemorrhage occurred during procedures known to carry a high bleeding risk also because haemostasis on the bone is currently considered difficult to achieve.

The analysis of RT in the bleeding events showed that the excessive blood loss occurred peri-operatively and that in each case the dose given ranged from low to very low (Table III), and were suspected to be insufficient to secure haemostasis in the setting of major surgery and during the period of highest bleeding risk. These data were confirmed by the ROC analysis, which indicated that haemostasis could be secured by single doses of at least 13 μg/kg and three or more administrations/day. The result obtained through the ROC analysis was in agreement with previous observations stemming from compassionate use studies or clinical observations (Bauer, 1996; Mariani *et al*, 1999).

Therefore, the low-dose RT schedule administered appears the most plausible explanation for the reported bleeding events.

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Table III. Major surgical interventions (unless otherwise stated treatment schedules were by bolus infusion).

Gender, Age and Intervention	Patient	RT d (*n*)	Total number of doses	Total dose (μg/kg)	Mean daily dose (μg/kg)	Range of doses	Adverse events
Orthopaedic surgery							
Total hip replacement	4	13	32	265	20·4	6·6–13·3	Bleeding
Total knee replacement	4	15	34	241	16·1	6·5–13	Bleeding
Bone tumour (forearm)	20	11	31	417	37·9	10–20	No
Right femoral fracture	33	2	2	24	12	12–12	No
Orthopaedic surgery	33	1	2	24	24	12–12	Bleeding
Surgery for Dupuytren	12	6	16	104	17·3	6·5–6·5	No
Neuro-, Head & Neck, Eye and ENT surgery							
Struma surgery	22	1	2	30	30	15–15	No
Adenotomy and tympanic-drainage	25	3	6	33·2	11·1	1·2–21·5	No
Cataract surgery	10	5	12	78	15·6	4·2–13	No
Exeresis of right parotid tail adenoma	28	1	1	20	20	20	No
Excision of fibroma of the tongue	34	1	2	60	60	30–30	No
Continuous infusion							
Ablation of cholesteatoma and tympanoplastic	14	18	–	1571	76·6	–	No
Adenectomy, mastoidectomy and tympanoplastic	9	6	–	163	10·0	–	No
Obstetric, Gynaecological and abdominal surgery							
Myomectomy	31	1	1	12	12	12	No
Hysterectomy & bilateral ovariectomy	2	11	29	436	39·6	11–22	No
Neoformation in the left testis	30	1	1	15	15	15	No
Haemorrhoid resection	18	3	4	80	26·7	20–20	No
Hernioplasty	24	1	3	90	90	30–30	No
Hernioplasty	23	1	2	30	30	15–15	No
Kidney Transplantation	16	16	37	672	42	10–45	No
Laparascopic removal of ovary cyst	19	1	2	40	40	20–20	No
Multiple gastric biopsies for lymphoma	13	1	1	18	18	18	No
Ablation of urinary bladder tumour	1	6	15	100	17	6·3–12·6	No
Cardiosurgery							
Valvular prosthesis implantation	27	1	1	87	87	87	No

Patients are numbered as in Table II.
ENT, Ear, nose and throat.

In this context, it appears important to discuss the results of a recent experimental work (Brummel Ziedins *et al*, 2004), in which very low rFVIIa doses (1–2 μg/kg/bw) were suggested to produce a competent haemostasis as measured by surrogate markers. However, this study was performed in a few selected FVII patients, in a non-bleeding state and the computerized models and the *ex-vivo* and *para-vivo* experiments can be hardly applied in the field of surgery.

Assuming that the observed bleeding episodes were due to insufficient doses of NovoSeven®, the fact that no haemorrhage occurred after the day of surgery in both severe and mild patients, may be explained by the accumulation of the infused factor, still haemostatically active, within the extra-vascular space (Hoffman *et al*, 2007) and/or to a progressively reduced bleeding risk.

Concerning Oral Surgery, in the eight cases treated by bolus infusion (Table IV), RT duration ranged from 1 to 4 d together with antifibrinolytics as concomitant medication without bleeding complications. 'Minor' surgical interventions and invasive diagnostic procedures are important elements of current medical practice. There are no publications providing evidence for the assessment of the bleeding risk in this important diagnostic and therapeutic area of modern medicine. Among the seven procedures performed (Table IV), RT, with the exception of one case, was given only on the day of the intervention. Bleeding did not occur in any of the cases, confirming that RT in this setting can ensure haemostasis even if confined to the first post-operative hours.

It has been matter of debate whether RT for surgical interventions should be limited to already symptomatic patients (Giansily-Blaizot *et al*, 2002). In our opinion, the absence of bleeding symptoms in the patient's history should not be the only factor used to assess the bleeding risk. Besides the severity of the clotting defect, the type of intervention, the setting (emergency or elective) and the presence of concom-

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Table IV. Minor Surgery (unless otherwise stated treatment schedules were by bolus infusion).

Gender, Age and Intervention	Patient	RT d (*n*)	Total number of doses	Total dose	Mean daily dose	Range of doses	Adverse events
Dental extractions							
Multiple dental extraction	3	4	9	110	27·5	11–22	Inhibitor
Teeth extractions	7	1	2	25	25	12·5–12·5	No
Tooth extraction	17	1	2	30	30	15–15	No
Multiple teeth extractions	26	1	1	30	30	30	No
Multiple teeth extractions	6	3	8	88	29·3	11–11	No
Tooth extraction	29	1	2	60	60	30–30	No
Multiple teeth extraction	11	3	6	44	14·7	7·3–7·3	No
Tooth extraction	15	1	2	40	40	20–20	No
Multiple teeth extractions	26	1	1	30	30	30	No
Continuous infusion							
Multiple dental extractions	1	6	–	26	5	–	No
Other minor surgical interventions and invasive diagnostic procedures							
Tonsillectomy	29	10	12	510	51	30–60	No
Bone marrow aspirate	8	1	2	20	20	20–20	No
Bone marrow biopsy	8	1	1	20	20	20	No
Ablation of subcutaneous cyst	5	1	3	60	20	20–20	No
Colonscopy ande polypectomy	32	1	3	36	36	12–12	No
Colonscopy and biopsy	21	1	1	6	6	6	No
Removal of sebaceous cyst	24	1	2	30	30	15–15	No

Patients are numbered as in Table II.
RT, replacement therapy.

Table V. Replacement therapy, main features.

	Surgeries *N*	Treatment d	Administrations	Dose (μg/kg/bw) Total dose	Daily dose	Single dose
All	38	3·5 (1–16)	7·6 (1–37)	103·4 (12–552)	31·9 (12–120)	18·7 (6·5–87)
FVII:C levels						
≤1%	9	5·8 (1–16)	14 (1–34)	142·5 (20–436)	27·3 (16·5–60)	13·5 (6·7–20)
>1–10%	13	4·1 (1–20)	9·5 (1–37)	117·6 (18–552)	27·4 (14·6–40)	15·2 (6·5–30)
>10–20%	16	1·7 (1–10)	2·6 (1–12)	69·8 (12–510)	38·1 (12–120)	24·4 (8·9–87)

Values given as mean (range).

itant illnesses may indeed play a role. It is also important to consider that an early or a late surgical bleed may jeopardize the outcome of a surgical intervention and induce the surgeon to evacuate the theatre. Safety of concentrates, namely in terms of viral transmission risk, is another element worthy of consideration.

In the present report focused on surgery, no cases of thrombosis were reported within the 30 d of follow up. This was the case, notwithstanding the number, variety and importance of the surgical interventions described and the wide array of treatment age and RT schedules (Tables III–V). This issue was evaluated in a previous publication, which described different types of thrombosis that occurred in a fashion independent of inherited thrombophilia (Mariani *et al* 2003). From this cohort the issue of thrombosis in patients with FVII deficiency undergoing surgery with rFVIIa coverage seems to be of scarce relevance, at least with this range of doses.

The other major adverse event of RT was the occurrence of an inhibitor to FVII. This complication was observed in one patient with a severe defect 30 d after a multiple dental extraction procedure (10 BU) (Table IV). The inhibitor titre peak was 18 BU.

In conclusion, RT with NovoSeven® for surgery in FVII deficient patients is effective and safe, provided that minimally effective doses are used. In the analyses performed in the present study, the minimally effective dose, calculated with reference to the highest risk bleeding period (the operation day), was estimated to be 13 μg/kg/bw (first dose) with at least two additional doses. This indication is valid especially for patients who undergo major surgical operations. Safety

1. **In conclusion, RT with NovoSeven Ò for surgery in FVII deficient patients is effective and safe, Anchor Name: high efficacy** *[Agency Switzerland m.waldis@fatzerimbach.ch]*

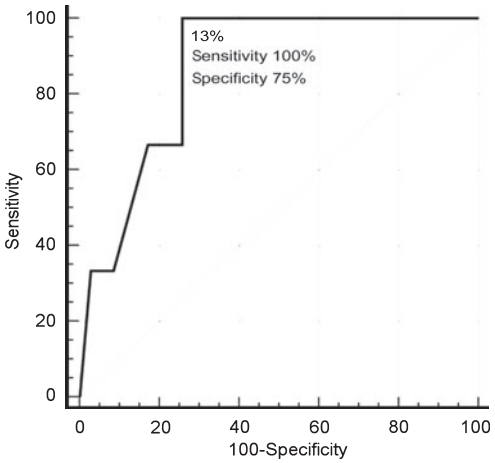

Fig 1. ROC curve analysis regarding the first dose during the operation day.

appears to be very good in terms of thrombosis risk, no matter the individuals' age, and it is important to bear in mind that those severe patients who are heavily treated may develop antibodies to FVII.

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[no notes on this page]