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Uncomplicated neurosurgical resection of a malignant glioneuronal tumour under haemostatic cover of rFVIIa in a severe haemophilia patient with a high-titre inhibitor: a case report and literature review of rFVIIa use in major surgeries

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Summary. The development of inhibitors following factor VIII replacement therapy is a serious complication in severe inherited haemophilia. Whereas significant experience, notably in orthopaedic surgery, is now obtained with the use of bypassing agents in haemophilia with high-titre inhibitor, new surgical challenges might occur due to patients' increasing life expectancy. A 56-year-old severe haemophilia A patient with a high-titre inhibitor was diagnosed for probable right temporoparietal malignant glioneuronal tumour on cerebral magnetic resonance imaging (MRI) (4 cm x 3 cm cerebromeningeal tumour with perilesional oedema and transfalcial herniation) requiring total resection. Then recombinant activated FVII (rFVIIa) was chosen as the haemostatic agent: bolus of 270 μg kg^{-1} every 2 h during the first 24 h, 180 μg kg^{-1} every 3, 4 and 6 h, respectively, at days 2–3, from days 4–10 and finally from days 11–15. Tranexamic acid was associated. Pre- and postoperative courses were uneventful, the surgical procedure being assessed at optimal haemostatic condition without any unusual haemorrhage on MRI controls, diffuse intravascular coagulation criteria or thromboembolic event. Intensive rFVIIa therapy has shown to be safe and effective in this first reported neurosurgery about a malignant tumour exhibiting to a high-bleeding risk notably in haemophilia with high-titre inhibitor. The use of lower doses of rFVIIa might have been possible; however, in the absence of accurate test for monitoring rFVIIa therapy, the potentially life-threatening complications of this procedure required maximum haemostasis with high rFVIIa doses.

Keywords: FVIII inhibitor, major surgery, malignant glioneuronal tumour, rFVIIa, severe haemophilia, tranexamic acid

Introduction

The development of inhibitors following factor VIII replacement therapy is the most serious treatment-related complication in severe haemophilia, complicating its management, and potentially resulting in increased morbidity and mortality in severe haemophilia patients [1]. Whereas significant experience, notably in orthopaedic surgery, is now obtained with the use of bypassing agents in patients with inhibitor [2,3], new and unexplored surgical challenges might occur, due to the increasing life expectancy of these patients [4–6]. Beside high-dose FVIII replacement that can be used when inhibitor titre is low [<5 Bethesda Units (BU)], two main bypassing products are usually used in high-titre (>5 BU) patients for the control or the prevention of

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bleedings: an activated prothrombin complex concentrate [aPCC (FEIBA®; Baxter, Vienna, Austria)] or a recombinant activated FVIIa [rFVIIa (NovoSeven®; Novo Nordisk, Bagsværd, Denmark)] product [7,8].

We have chosen rFVIIa as haemostatic cover of a surgical resection of a brain tumour responsible for intracranial hypertension with a working diagnosis of glioblastoma in a severe haemophilic adult patient with a persistent high-titre inhibitor. As, to the best of our knowledge, there is not a protocol scheme of bypassing agents use for neurosurgical interventions in high-titre inhibitor haemophilia, this case being the first reported, we fully described the scheme of rFVIIa haemostatic cover used, the patient management and favourable outcome.

Patient and methods

The patient was a 56-year-old male with severe haemophilia A (bodyweight 75 kg), with an historical peak inhibitor titre of 40 BU and chronic non-active hepatitis C. He has experienced several psoas haematomas and haemarthroses which were treated with both aPCC and rFVIIa with equivalent satisfactory efficacy. Finally, because the profile of aPCC infusions intervals was best adapted to the patient's lifestyle (frequent business trips), he preferred aPCC on demand and brief intermittent prophylactic treatments for the last 8 years. The patient had never been proposed for immune-tolerance as he lives mostly in the Democratic Republic of Congo (of which he is a native), and travels to France for medical necessities only; the genetic singular anomaly of FVIII corresponds to a deletion involving exons 2–6.

The patient was recently diagnosed for probable right temporoparietal glioblastoma on cerebral magnetic resonance imaging (MRI) (4 cm × 3 cm partially necrosed tumour with meningeal thickening, important peri-lesional oedema and transfalcial herniation) requiring total surgical resection.

At admission, the inhibitor titre was 16 BU and surgery was performed during the following 3 weeks. The monitoring of the inhibitor titres showed stable levels about 12–16 and 15–20 BU respectively for the previous 2 years of rFVIIa use and the last 8 years of aPCC use. Because of headaches and pyramidal signs, anti-oedematous (oral cortisone 1 mg kg^{-1}) and anticonvulsive (lamitrigine) therapies were initiated. Rituximab treatment (two doses of 1000 mg at day 1 and day 14) was initiated in an attempt to lower the inhibitor titre below 5 BU, allowing the surgery to be performed with high doses of FVIII. On the day of surgery, the inhibitor titre was 10 BU (with a global assessment corresponding to a type I kinetic profile), leading to the choice of rFVIIa as the haemostatic agent during surgery with the following dosing schedule: bolus injections of 270 μg kg^{-1} every 2 h, initiated 1 h preoperatively and during the first 24 h, followed by 180 μg kg^{-1} every 3 h on days 2 and 3, 180 μg kg^{-1} every 4 h on days 4–10, and finally 180 μg kg^{-1} every 6 h on days 11–15. The antifibrinolytic tranexamic acid (3 g every 24 h intravenously) was given concomitantly; the use of any concurrent medication that could cause platelet or haemostasis dysfunction was forbidden.

The main haemostatic objectives were: to keep the prothrombin-time (PT) below normal range until complete cicatrization of the surgical wound, estimated at the fifteenth postoperative day; to carefully monitor thromboembolic and diffuse intravascular coagulation events, by clinical assessment and repeat evaluation of platelet count, fibrinogen level, DDimer and plasma soluble monomer complexes. Prothrombin time and fibrinogen level were performed on a photo optical coagulometer (ACLTop, Instrumentation Laboratory) with a recombinant thromboplastin (Innovin, Dade Behring, Marburg, Germany) and thrombin reagent (Dade Behring) respectively. DDimer were determined using a latex agglutination slide tests (D-Di Test, Diagnostica Stago, Asnières, France) allowing a rapid semi quantitative determination of DDimer in plasma. Ethanol gelation method was used to look for the presence of plasma soluble monomer complexes.

Results and discussion

A total of 90 infusions of rFVIIa were used within 15 days, corresponding to a total dose of 1 296 mg (17 280 μg kg^{-1}) and a total cost of 821,145.50 Euros.

Pre-, peri- and postoperative courses were uneventful, with the neurosurgeon judging the surgical procedure at optimal haemostatic condition without unusual haemorrhages. Almost complete removal of the brain tumour after craniotomy was achieved, leaving behind some residual meningeal involvements. Start and repeated coagulations tests and platelets counts never showed criteria of disseminated intravascular coagulation during the entire rFVIIa treatment (Table 1). The haemogram remained normal, with the exception of a slight and transient decrease of haemoglobin and platelets, both being attributed to the surgical procedure, and no blood transfusion was required.

Histological examination of the removed tissue leads to the conclusion of a malignant glioneuronal

[no notes on this page]

Table 1. Haematological parameters monitored under high doses of rFVIIa.

	Day 1 before rFVII administration	Day 1 after rFVII administration	Day 2	Day 3	Days 4–8	Days 9–10	Days 11–15
rFVIIa bolus	270 μg kg^{-1} 2 h^{-1}	270 μg kg^{-1} 2 h^{-1}	180 μg kg^{-1} 3 h^{-1}	180 μg kg^{-1} 3 h^{-1}	180 μg kg^{-1} 4 h^{-1}	180 μg kg^{-1} 4 h^{-1}	180 μg kg^{-1} 6 h^{-1}
Haemoglobin (g dL^{-1})	13	12.3	12.1	11.5	11.3–12	12–12.3	12–13.2
Platelets (10^9 L^{-1})	210	250	180	140*	129* (Day 8)–250	180–210	270–350
Prothrombin time (NR: 9.4–11.9 s)	9.6	<6.4†	<6.4†	<6.4†	<6.4†	6.4–6.6	6.5–6.8
Fibrinogen (NR: 2–4 gL^{-1})	2.1	2.3	2.8	2.1	1.4* (Day 6)–2.2	2.2–2.7	2.4–2.8
D-Dimers (NR: <1 μg mL^{-1})	<1	<1	1–2*	<1	–<1 (Days 4, 6 & 7) –1–2* (Day5)	<1	<1
Soluble fibrin monomer complexes test	–	Negative	Negative	–	Negative	–	–

NR: normal range; *slight, no concomitant and transient abnormal parameters without grouped criteria of diffuse intravascular coagulation; † Very low coagulation time, outside the limit of the coagulaometer.

tumour with hypervascularization. Postoperative clinical examination showed no neurological sequelae. Successive cerebral computed tomographies (CT) and MRI controls showed no unusual features, with the exception of residual cerebral oedema and some meningeal thickening (Figs 1 and 2), as well as the usual initial postoperative blood filling of the surgical cavity and a small surgery-related subdural haematoma on the first iconographies. No thromboembolic events were observed. The patient is currently undergoing radio-chemotherapy under an antioedematous dose of 15 mg of cortisone, without any haemostatic prophylactic regimen, and without any cerebral haemorrhagic event within the 11-month follow-up. The inhibitor titre decreased to 4 and 1.9 BU, 3 and 7 months respectively, after rituximab therapy and without aPCC use for bleeding episodes; no bleeding episode occurred. The profile of evolution of historical titres and the profile of actual titration kinetic of the inhibitor allowed the exclusion of an eventual additional auto-immune acquired FVIII inhibitor related to the malignancy.

Prolonged and initial high doses rFVIIa therapy in this neurosurgical case was shown to be both safe and effective; this procedure was associated with a high risk of bleeding due to the nature of the surgery as well as the important vascularization of this type of brain tumour which has the greatest extent of tumour angiogenesis among a variety of human malignancies [9]. The use of lower doses of rFVIIa as well as a shorter duration of treatment might have been possible. However, the urgent and potentially life-threatening haemorrhagic nature of this procedure required maximum haemostasis and haemostatic protocols for this type of surgery in haemophilia patients with high-titre inhibitors were not available. Furthermore, the haemostatic scheme used here is not very different from some rFVIIa schedules used in major orthopaedic surgeries where per- or posthaemorrhagic events do not have the dramatic and severe life-threatening consequences carried by intracranial bleeding.

Quintana-Molina *et al.* reported four surgical procedures under rFVIIa cover (including two cases of hip and knee replacement, one case of craniotomy and one case of corneal transplant respectively in persistent inhibitor haemophilic patients). Initial doses of rFVIIa ranged from 90 to 300 μg kg^{-1} and total doses ranged from 1440 to 72 000 μg kg^{-1} (Table 2), the knee replacement procedure having been complicated by bleeding that led to a considerable prolongation of days of treatment and the highest total dose used [10]. The third case of major surgery was a craniotomy that had been complicated

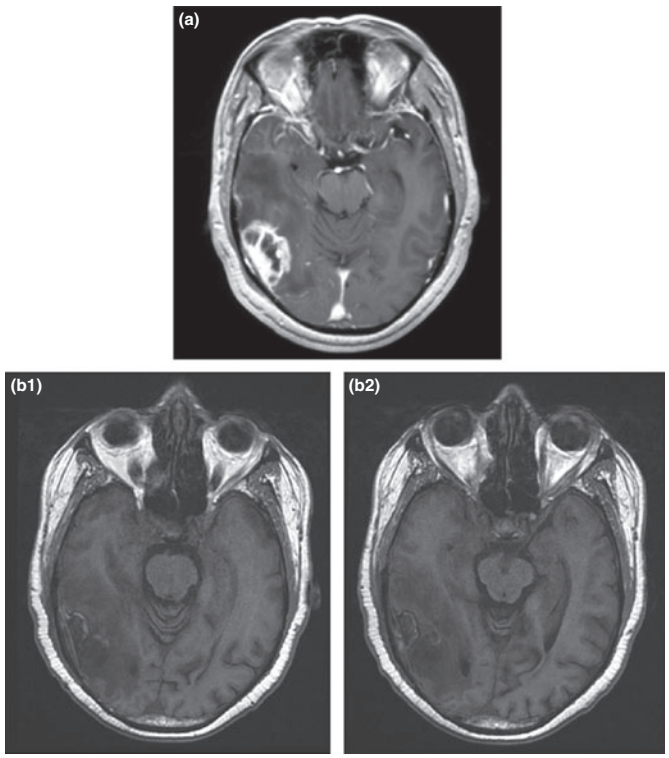

Fig. 1. Cerebral T1-weighted MRI: axial sequence at the level of cerebral trunk (just above the pavilions of ears). Panel a: presurgical MRI: right perilesional oedema with right ventricular narrowing and partially necrosed temporoparietal tumour mass with thickened wall, invading meningeal structures (high gadolinium enhancement sequence). Panels b1 and b2: sixteenth postsurgical day MRI: right temporoparietal collapsed postsurgical virtual cavity with slight thickened meningeal structures (increased T1 MRI signal), residual perilesional oedema and right ventricular narrowing.

by haemorrhage, leading to replacement of rFVIIa by aPCC, but for which the doses used were not specified. In the fourth case, a total dose of only 1440 μg kg^{-1} was sufficient for a corneal transplant, and here we question the high or low haemorrhagic character of this surgical procedure. Rodriguez-Merchan *et al.* report 16 major orthopaedic surgeries under rFVIIa cover where mean doses were 150 μg kg^{-1} every 2 h (range 90–200 μg kg^{-1}) for the first day, relayed by continuous infusion for 3–7 days; three procedures where rFVIIa doses were 90 μg kg^{-1} (two total knee arthroplasties, one fixation for femoral neck fracture) have shown severe bleedings (two haemarthrosis and one haemophilic pseudotumour), these complications having been clearly related to an insufficient perioperative haemostasis [2,11].

Table 2 shows the comparative daily doses of rFVIIa used in this report and the literature [10–14]; it appears that only the total of day 1 is significantly higher in the present scheme; the total doses of the following days being equivalent to that used in the literature for elective high-risk bleeding surgeries (total doses ranged from 4320 to 24 000 μg kg^{-1}), excluding the corneal transplant procedure and a prolonged therapy of knee surgery complicated by bleeding reported by Quintana-Molina *et al.* Considering the cumulative dose at day 10 that could be sufficient in this neurosurgery, consumption of rFVIIa appeared very near that used in major orthopaedic surgeries that pursue the haemostatic cover until this date (Table 2). Finally, considering dosages of rFVIIa bolus of at least of 90 μg kg^{-1} (range 90–300 μg kg^{-1}) essential in major orthopaedic surgeries, 37.5% (12/32 procedures) showed bleeding complications, essentially with the lowest dosages (Table 2).

In his review, Obergfell *et al.* identified 12 articles documenting the use of rFVIIa in haemophilic patients with inhibitors undergoing essentially major orthopaedic surgery, covering a total of 80 procedures [3]. Dosages were not uniform, but for most of them the schedule used was rFVIIa (initial bolus ranged from 90 to 200 μg kg^{-1} every 2 h), relayed by continuous infusions or by bolus with reducing dosage or increasing dosing interval. These authors

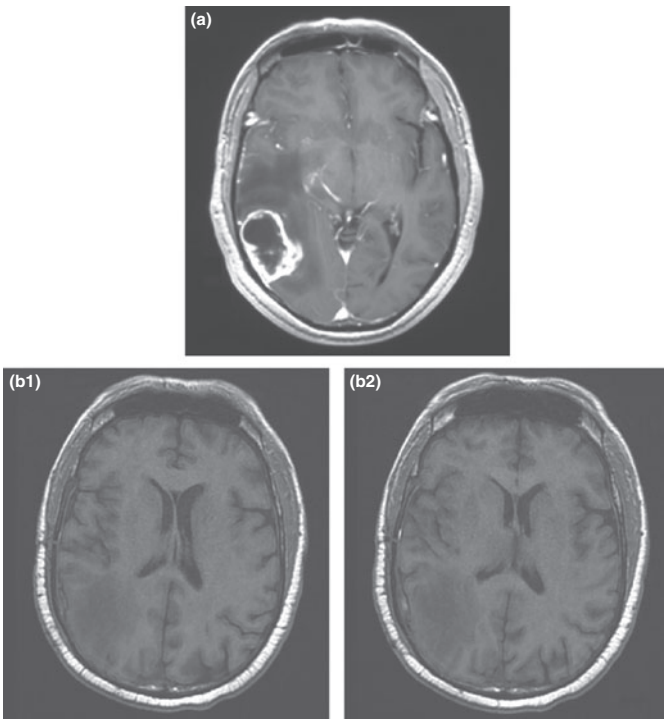

Fig. 2. Cerebral T1-weighted MRI: axial sequence at the level of frontal sinus. Panel a: Presurgical MRI: right massive perilesional oedema with narrowing and displacement of ventricular system, partially necrosed temporoparietal tumour mass with thickened wall, invading meningeal structures (high gadolinium enhancement sequence). Panels b1 and b2: Sixteenth postsurgical day MRI: residual thickened meningeal structures (increased T1 MRI signal in panel b2), net decrease of both perilesional oedema in healed surgical area and intracranial hypertension signs.

also report good efficacy, with the rare insufficient haemostatic results being related to inadequate amounts of rFVIIa.

Considering non-haemorrhagic adverse effects, only two cases of thrombophlebitis and one case of disseminated intravascular coagulation (DIC) have been reported; the latter occurring in the context of infected pseudotumour excision, the infectious process likely an additional and essential favourable cause of this activated coagulation condition [11,15]. Thus, Rodriguez-Merchan *et al.* proposed that for elective major orthopaedic surgery in inhibitor patients, the standard regimen should be 150–200 μg kg^{-1} every 2 h for the first 48 h with increasing intervals between doses after this first postoperative period. Lower doses and continuous infusion both seemed less efficient; this last procedure is not yet approved and has been described as responsible for few bleedings and related to the only case of DIC occurring during rFVII therapy (Table 2) [11,13]. Rajic *et al.* reported a successful supracondylar amputation of a lower limb with a compartment syndrome under rFVIIa cover with bolus dosages varying from 90 to 180 μg kg^{-1} every 2 h for the first five postoperative days; the bolus intervals were gradually extended up to 6 h until the fifteenth postoperative day. This procedure was a success but an intra-operative blood loss led to a drop in haemoglobin level from 130 to 90 g L^{-1}, requiring one unit of packed blood transfusion, followed by an oozing during several days. This relative significant per- and postsurgical bleeding is not, however, allowable in the neurosurgical context of our patient with a pre-existing symptomatic intracranial hypertension on massive cerebral oedema.

Considering the choice between aPCCs and rFVIIa, several reasons lead us to choose the second in this present case, even though both drugs showed almost equivalent satisfactory response for previous classical haemorrhagic sites in haemophilic patients. First, in the perspective of possible need of another surgical procedure or chemotherapy with increased risk of bleeding because of related thrombocythopenia, we tried to preserve the possibility of later FVIII therapy by avoiding an enhancement of the inhibitor by aPCC use. The second reason is based on safety and experience of bypassing agents in major surgical procedures, the reported use of aPCC being relatively

Table 2. Comparative of rFVIIa consumption for the present neurosurgery and elective high-bleeding risk surgeries requiring high dosages use in the literature.

		Daily dose of rFVIIa (μg kg^{-1})								
	Dose of initial bolus	Day 1	Day 2	Day 3	Days 4–8	Days 9–10	Days 11–15	Bolus number	Total cumulative dose (μg kg^{-1})	Haemostatic outcome
Present report (one patient)	270 μg kg^{-1} (brain neurosurgery with craniotomy)	3240 (270 2h^{-1})	1440 (180 3h^{-1})	1440 (180 3h^{-1})	1080 (180 4h^{-1})	1080 (180 4h^{-1})	720 (180 6h^{-1})	90	17 280 (cumulative dose at Day 10: 13 680)	Success
Rodriguez-Merchan [11] (eight patients)	90–200 μg kg^{-1} (16 major orthopaedic procedures)	1080–2400 (90–200 2h^{-1})	Daily continuous infusion of 1080for 3–7 days (45 μg kg^{-1} 1h^{-1})			–	–	NA	4320–9960	Two haemarthrosis and one pseudotumour† with successful surgical resumptions
Quintana-Molina [10] (four patients)	Patient 1: 300 μg kg^{-1} (hip replacement)	–	–	–	–	–	–	75	12 300	Success
	Patient 2: 240 μg kg^{-1} (knee replacement)	–	–	–	–	–	–	300	72 000	Haemorrhage, then prolongation of therapy
	Patient 3*: (craniotomy)	–	–	–	–	–	–	–	–	Haemorrhage, then rFVIIa* relayed by aPCC
	Patient 4: 90 μg kg^{-1} (corneal transplant)	–	–	–	–	–	–	–	1440	Success
Perez [12] (one patient)	150 μg kg^{-1} (hip arthroplasty)	‡ (Two initial bolus, then 120 2.5h^{-1})	‡ (120 2.5h^{-1})	720 (90 3h^{-1})	Bolus of 90 3h^{-1} (days 4–5), then continuous infusion of tempered doses (days 6–17)			NA	6300	Success
Ludlam [13] (nine patients)	90 μg kg^{-1} (knee replacements)	One initial bolus, then fixed dose of daily continuous infusion of 1200 (50h^{-1}) for a median of 20 days						NA	Median: 24 000 (cumulative dose at Day 10: 12 000)	6/9 immediate postoperative haemorrhage requiring a novel bolus
Rajic [14] (one patient)	90 μg kg^{-1} (limb amputation)	Variable bolus dosages of 90–180 2h^{-1} from day 1 to day 5, then the bolus intervals were gradually extended up to 6 h until the fifteenth postoperative day						*	*(cumulative dose at Day 10: >10 000)	Success but intra-operative bleeding (requiring blood transfusion) and several postoperative days of oozing

*Unspecified data.
†Lower initial bolus of 90 μg kg^{-1}.
‡Vague timing of initial bolus interval and total daily doses; NA, not applicable.

minimal despite the fact that the latter has been available for more than 20 years, probably because of a supposed higher risk of thromboembolic complications compared with rFVIIa, considering the high doses that may be necessary in these situations [3,11]. These lower thromboembolic complication or DIC risks might explain why rFVIIa is the only tried bypassing agent for severe bleedings in non-haemophilic patients. Finally, the last argument for preferring rFVIIa in this case is based on the richness of cerebral parenchyma in tissue factor [16], which allows hope for a great efficacy of rFVIIa for bleeding control in neurosurgery.

To the best of our knowledge, this is the first reported case of a neurosurgical procedure, notably for a hypervascular malignant brain tumour, in a severe haemophilia patient with high-titre inhibitor. This high dosage rFVIIa cover is unpublished but takes into account the experience acquired in major orthopaedic surgeries and is used in a setting where the surgical bleeding risk was assessed as being among the highest. Thus, it seems that daily repetitive bolus of up to 150–200 μg kg^{-1} are required for major surgeries [11], notably in the first postoperative period, and especially when haemodynamic or local conditions do not allow the risk of an additional bleeding. Specific, reproducible and reliable thrombin generation tests [17] are awaited to optimize the choice, the optimal dosage and appropriate timing of administration of bypassing agents, adapted to both the general profile of individual bleeding risk and type of surgery. A best appropriate dosage and monitoring of these drugs could reduce the high cost of surgery in haemophilia especially with inhibitor, this care being cost prohibitive in several countries and/or social health protection systems.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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