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Case report

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Thromboelastography in pre-surgery monitoring in Hemophilia A with high inhibitor titer: case report and literature review

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Abstract

The development of factor VIII inhibitors (allo-antibodies) continues to be a major complication in the management of severe forms of hemophilia A, especially as far as treatment and treatment response monitoring is concerned. The need to implement a reliable laboratory assay is all the more obvious if major surgery occurs, when conventional tests (activated partial thromboplastin time APTT, prothrombin time PT, factor VIII level) are of no avail and there is a very fragile balance between bleeding and thrombosis.

We report the case of a 32 year-old patient diagnosed with severe Hemophilia A, referred to the Comprehensive Center for the Diagnosis and Treatment of Hemophilia of the Fundeni Clinical Institute for a multidisciplinary assessment in view of a total left hip arthroplasty due to aseptic necrosis of the femoral neck.

Workup showed a high inhibitor titer (>200 BU). Taking into consideration the interindividual variability of the response to bypassing agents, as well as the bleeding risk associated with a major orthopedic surgery, we used thromboelastography (TEG) to assess the patient's response to aPCC (activated prothrombin complex concentrate) and rFVIIa (activated recombinant factor VII). The findings helped select the optimal replacement scheme to ensure perioperative hemostasis.

Keywords: *severe hemophilia A, inhibitors, thromboelastography, bypassing agents*

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Introduction

Hemophilia A is a field which has seen significant progress over the last decades, especially concerning genetic testing, new factor VIII products, and gene therapy. All these have contributed to increase survival and improve quality of life in hemophilia patients. However, they have not helped overcome the development of allo-antibodies (inhibitors) against factor VIII concentrates, a major complication in hemophilia, with loss of response to standard therapy and increased bleeding risk (1,2). Patients with high inhibitor titer have a higher frequency and

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severity of joint bleeding and more severe joint damage, with a significant impact on morbidity and quality of life.

Bypassing agents represent the therapeutic option in hemophilia A with high inhibitor titer: activated prothrombin complex concentrates (aPCC) or recombinant factor VII (rFVIIa), with demonstrated similar efficacy (80-90%) in the treatment of bleeding episodes (3). Studies have demonstrated that there is a high intra- and inter-individual variability in response (4,5), but unlike standard factor VIII products, conventional laboratory tests are not able to evaluate the response to bypassing agents (6,9,17). The ideal laboratory assay should be simple, accessible, easy to use, and to yield a fast and reproducible result (7,22). Global tests for coagulation, thromboelastography (TEG), and thrombin generation assay (TGA) are the only available assays to allow the qualitative evaluation of the hemostatic response to bypassing agents, having received increased interest over the last years (1,2,8-22). Apart from clinical response, the two assays provide a real support in therapy customization for inhibitor patients, particularly in delicate situations, such as major bleedings or surgery (18).

If initially TEG was not widely used due to technical limitations and lack of standardization, this has changed thanks to technical progress and digitization of TEG curves (19,20). Nowadays, TEG is increasingly useful in multiple circumstances, from predicting transfusion requirements in liver transplant, heart surgery or neurosurgery, to the monitoring of patients with hemophilia, rare clotting disorders or anti-clotting medication (15,21-24).

Case description

We report the case of a 32 year-old patient, registered at Brasov Hematology Hospital with severe hemophilia A since the age of 3 months, chronic hemophilic arthropathy affecting both knees, elbows, left hip (target joints), with joint deformity, muscle hypotrophy, and limited mobility. The patient was receiving infrequent on-demand treatment with plasma or recombinant factor VIII concentrates. From the age of 16, the patient presented progressive pain in his left hip, with joint damage, decreased range of motion (ROM), and assisted walking.

During the last year, the pain and bleeding episodes increased in frequency and intensity, requiring repeated hospitalization. Also, the patient reported a decrease in the efficacy of the factor treatment, but no inhibitor was detected at that moment.

Considering the continuous pain, the limitation of functionality, and the impact on quality of life, an orthopedic examination was recommended, however, it was not performed due to poor compliance of the patient.

A pelvis MRI performed in December 2017 detected an almost complete necrosis of the left femoral neck, with multiple cystic joint fluid accumulations.

In January 2018, the patient was referred to the Comprehensive Center for the Diagnosis and Treatment of Hemophilia in Fundeni Institute for a complete assessment before undertaking the orthopedic surgery. The patient was in moderate clinical condition, without active bleedings, with chronic pain in his left hip, limited range of motion (flexion [F] 90°, external rotation [ER] 20°, internal rotation [IR] 10°), bilateral hypotrophy of gluteal muscles, left knee with valgus deviation and decreased flexion - extension. Due to the advanced joint damage, the patient needed crutches for walking. He had a body weight of 80 kg.

Laboratory findings showed prolonged activated partial thromboplastin time (APTT 97 sec), a factor VIII level of 0% and an inhibitor titer > 120 BU. The virologic assay detected an HCV-RNA level of 6,199,000 IU/mL.

The detection of the high inhibitor titer hindered the management of this patient, both as far as

treatment and its monitoring is concerned. The patient was naïve to bypassing agent treatment, so we were unable to select the optimal scheme for pre-surgical treatment without an accurate assessment of the patient's response to each of the two products.

Material and methods

We used thromboelastography (Haemoscope 5000 Thrombelastograph analyzer and TEG Analytical Software). Blood was sampled in 2 sodium citrate 3.2% test tubes (BD Vacutainer 9 NC 0.109 M), from a peripheral vein, using a 21G needle, following minimal stasis. After 30 minutes at room temperature, 1 ml of the total blood amount was mixed in the kaolin tube, followed by the transfer of 340 mcL into the cup together with 20 mcL of calcium chloride. Blood samples were collected before the administration of the two products (rFVIIa 100 mcg/kg body weight BW; aPCC 100 IU/kg BW), after 30 minutes and 1 hour respectively (Table 1). The two trials were performed on different days (aPCC was trialed >24 hours following rFVIIa to allow full clearance of the latter from the body).

All the test results and images of the TEG are published with the patient's consent.

Results showed that the two bypassing agents had comparable efficacy, with no significant differences between the parameters tested (appearance mildly in the favor of aPCC). (Figure 1A,B)

Since the patient was scheduled for surgery within 2 months and taking into consideration the joint status and the recurrent bleeding episodes, we decided to initiate aPCC prophylaxis in a dose of 3000 IU/day, 3 days/week until surgery. Within 2 weeks, the patient reported adverse reactions following administration of aPCC (performed according to the product information by healthcare specialists): dyspnea, intense headache, palpitations, and increased systolic blood pressure (SBP 180 mmHg). The course was slowly favorable under medication, but the patient further refused aPCC use.

Considering the side effects occurring during prophylaxis (at a low aPCC dose, less than 50 IU/kgBW kilograms of body weight), a decision

Table 1. Laboratory test results before and within 30 minutes and 1 hour from the administration of rFVIIa and aPCC respectively. At 3 hours, only routine clotting tests were performed.

	Normal range		Before	At 30 min.	At 1 hour	At 3 hours
APTT (sec)	26-40	rFVIIA	85	56.1	59.7	62.1
		aPCC	83.9	65.9	64.1	74.2
R (min)	2-8	rFVIIa	97.2	20	15.2	NP
		aPCC	53.9	14.7	18.2	NP
K (min)	1-3	rFVIIa	ND	2.9	6	NP
		aPCC	24.9	2.4	2.5	NP
α angle(degrees)	55-78	rFVIIa	ND	58.4	40.1	NP
		aPCC	9.5	60.9	59.2	NP
MA (mm)	51-69	rFVIIa	ND	77.4	74.4	NP
		aPCC	47.1	79.7	76.3	NP

aPCC: activated prothrombin complex; APTT: activated prothrombin time; K: K value; MA: maximum amplitude; ND: non-detectable; NP: not performed; R: response time; rFVIIa: recombinant activated factor VII

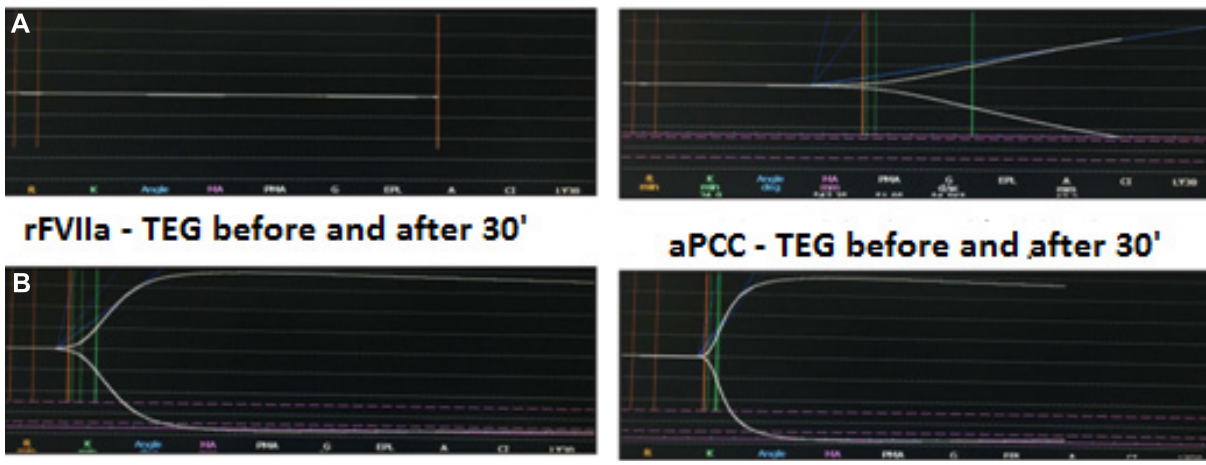

Fig 1. TEG before (A) and 30 minutes after (B) the administration of rFVIIa and aPCC

was made to use rFVIIa during the perioperative period, despite inconveniences related to the administration of doses at short intervals and costs. We followed the most recent international guidelines and protocols published in the literature (25).

Left hip arthroplasty was performed on March 29th. Pre-surgical hemoglobin level was 12.4 g/dL, INR 1.17, APTT 90.2s. Elaborate and firm maneuvers were necessary to remove the femoral neck from the acetabula due to advanced joint damage, osteosclerosis, and local fibrosis. The blood loss during surgery was similar to a non-hemophilia patient (~ 300 mL).

Post-surgery, the patient received rFVIIa according to the treatment plan (90 mcg/kgBW ~7 mg every 2 hours), with consistent factor VII levels of more than 300% and AP>180%. However, on day +2 the patient presented a decrease in hemoglobin level (7.5g/dL), without significant wound bleeding (~350mL within 24 hours on the drain tube), but with swelling of the thigh, with limited mobility. The patient received 2 units of packed red cells. The clotting tests indicated a factor VII level >300% (before dosing), APTT 67.8s, Fng 653 mg/dL, AP >180%; platelets 165,000/mm^3, while thromboelastography showed R 13.3 min, K 3.2 min, α angle 50.7°, MA 72.9 mm (Figure 2).

As a result, rFVIIa was continued every 2 hours for 2 additional days, and the dosing interval was gradually increased to 3 and 4 hours. Starting day +6, the patient received 6 mg of rFVIIa every 4 hours. The course was favorable, with an increase in hemoglobin level, no bleeding and improved joint range of motion. He was discharged from the Orthopedics department on day 7 and continued the administration of rFVIIa at home, 6 mg every 4 hours over 3 days, then every 6 hours over 3 days, and every 8 hours over 3 days. Over the following months, the patient continued the intermittent prophylaxis with rFVIIa and medical rehabilitation.

Discussions

Patients with hemophilia and high inhibitor titer have a poor joint status in comparison with inhibitor-free patients, due to repeated joint bleeding and treatment challenges. Total arthroplasty can significantly improve the quality of life in these patients; however, the associated bleeding risk may exceed the benefit (25). If ~20 years ago the recommendation was to preserve major orthopedic surgery only for urgent cases in he-

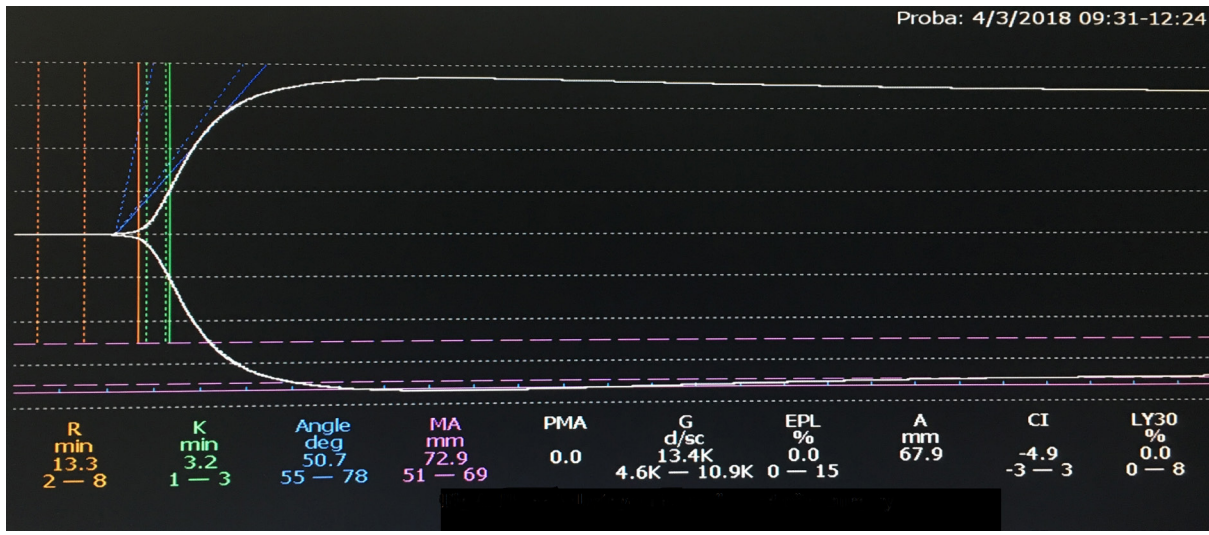

Fig. 2 TEG performed after surgery

mophilia patients with high inhibitor titer, the increased availability of bypassing agents allowed the access of all patients to elective orthopedic surgeries. Clinical studies have shown that the two products have similar efficacy in controlling bleeding (1,5), however, rFVIIa is associated with a lower risk of thrombotic complications and more convenient administration as compared with aPCC (bolus IV versus low infusion rate). High costs, shorter half-life (almost 2.6 h), and the need to administrate every 2-3 hours over several days may be counted among the disadvantages of rFVIIa therapy. As far as efficacy is concerned, there is a high inter-individual variability of patient response to each product (FENOC study) (1,5) and most studies focused more on the efficacy in joint bleeding control, and less on the pre-surgical setting, when the bleeding risk is higher. As consequence, it is necessary to select the optimal treatment scheme based on the individual anamnestic response, personal experience, pharmacy availability, and *in vitro* testing of hemostasis. Personalized therapy thus contributes to the optimization of the cost/efficacy balance by avoiding inappropriate dosing (higher or lower doses) and to the selection of the most efficient product.

Currently, thromboelastography has become an indispensable technique for monitoring the response during surgery in patients with high inhibitor titer. It is a laboratory test which studies the clotting process from the initiation of clot formation until lysis and assesses the dynamics and intensity of the process.

In our patient, we were unable to use either the anamnestic response or personal experience to guide our treatment decision because we were confronted with a newly diagnosed case of hemophilia with high inhibitor titer, the second case in our practice of total arthroplasty in a patient with inhibitors. Therefore, the accurate assessment of replacement therapy efficacy was necessary. As a result, we used thromboelastography to assess the patient's response to the two available products. Although aPCC replacement offered multiple advantages (TEG results which were mildly in favor of aPCC, lower cost, convenient administration), finally the choice was driven by the patient's preferences and tolerability. The plan for the pre-surgery administration of rFVIIa followed international recommenda-

tions and guidelines (25) and we consider that post-surgery bleeding resulted from local causes (laborious maneuvers during surgery due to the advanced joint ankylosis) rather than from lack of efficacy of the therapy. Generally, we consider this surgery to be a success of the interdisciplinary collaboration (hematologist, hemostasis laboratory, and orthopedist).

Conclusions

This case demonstrates the challenges associated with the assessment of a severe hemophilia patient before major surgery (total hip arthroplasty). First, factor VIII levels and inhibitor testing should be performed whenever necessary (loss treatment response, prior to major surgeries), in all hemophilia treatment centers. Second, a high inhibitor titer raises questions concerning peri-surgery replacement therapy, as far as cost and monitoring of treatment response to the two available bypassing agents is concerned. Interindividual variability, as well as the scarcity of laboratory tests providing an appropriate evaluation of the hemostatic efficacy of treatment prevents these patients from receiving orthopedic surgery in our country.

Current studies have shown that, although the two drugs have similar efficacy, response varies from one individual to another; therefore, it is mandatory to identify a specific, standardized laboratory test which can facilitate easy monitoring of hemostatic response. Thromboelastography which is a relatively accessible technique to explore the global process of clotting may be the solution.

Abbreviations

aPCC - activated prothrombin complex concentrate
APTT- activated partial thromboplastin time
BU - Bethesda units
BW – body weight
CI - clot index
CLI - clot lysis index
ER - external rotation
F - flexion
HBsAg-hepatitis B virus surface antigen
HCV antibodies - antibodies against hepatitis Cvirus
INR- international normalized ratio
IR - internal rotation
IU- international units
kgBW- kilograms of body weight
Ly30- fibrinolytic activity within 30 minutes from MA
MA - maximum amplitude
mcl- microliter
PT - prothrombin time
R - response time
rFVIIa - recombinant activated factor VII
ROM - range of motion
SBP - systolic blood pressure
TEG - thromboelastography
TGA - thrombin generation assay

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Authors' contributions

MB – conceptualization, original draft preparation, data collection, interpretation of data, writing, resources
VU – performing coagulation assays, interpretation of data, supervision, implementation of methodology, resources, review
GG, EC, CC– performing coagulation assays, interpretation of data
HO – performing surgical procedure, data collection
DC – supervision, design, review & editing

Conflicts of interest

The authors declare that they have no conflict of interest.

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