Research Article

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Combination of novoseven and feiba in hemophiliac patients with inhibitors

Abstract: The aim of this study is to investigate the effective therapeutic combination of recombinant VIIa(Novoseven) and factor eight inhibitor bypass activity(FEIBA) drugs for the bleedings of adult hemophiliac patients with inhibitors.19 bleeding episodes of 5 hemophilia A patients who were using bypassing agents and followed-up between 2008 and 2016 in Hacettepe Hematology Department were analyzed retrospectively. In 11, 5 and 3 bleeding episodes, FEIBA, recombinant factor VIIa and FEIBA+recombinant factor VIIa were given to the patients, respectively. The treatment durations differed between 1 and 14 days depending on the bleeding and clinical course of the patients. Generally the treatment with bypassing agents was successful, and only in one patient who had elbow hematoma encountered serious bleeding which was taken under control by switching the bypass agent. We offer a different approach because of three reasons. Firstly, in our protocol we start the treatment with recombinant factor VIIa for the first three days. Secondly, our protocol is adjusted to consider health economics. Thirdly, we extended the time interval between doses of both bypassing agents without increasing bleeding risks because the half-life of both agents enables us to modify the protocol with more flexibility. To conclude, we have evaluated our clinic's data about hemophilia A patients with inhibitors and we offer a different protocol in the management of bleeding episodes for these patients.

Keywords: Hemophilia; Inhibitors; FEIBA; Recombinant VIIA

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1 Introduction

The hemophilias are a group of associated bleeding disorders that are inherited most commonly. Hemophilia A refers to factor VIII deficiency. Cases with hemophilia encounter bleeding incidents that are treated with replacement of the absent factor. Development of an inhibitor is one of the complications of hemophilia treatment. It usually follows the initiation of replacement therapy. Actually, the inhibitors are antibodies (primarily IgG) directed against the specific absent factor. The development of inhibitors is more frequent in cases with hemophilia A than in those with hemophilia B. The inhibitors are more likely to develop in cases with severe disease. The degree of inhibitor response is detected in Bethesda units (BU). High responder patients generally have five or more Bethesda units and these inhibitor levels can persist for a long time even when there is no re-exposure [1,2]. On the other hand, low responder patients always have inhibitor levels less than 5 BU [3]. High responder patients generally need bypassing agents, whereas low responder cases usually have treatment answer to factor VIII replacement therapy [4]. In approximately 25 to 30 percent of cases with severe hemophilia A, Factor VIII inhibitors were detected [5,6]. Factor VIII inhibitors are not frequently encountered in moderate or mild hemophilia A cases [7]. The aim of this study is to investigate the effective therapeutic combination of recombinant VIIa (Novoseven) and factor eight inhibitor bypass activity (FEIBA) drugs for the bleedings of adult hemophiliac patients with inhibitors.

2 Methods

19 bleeding episodes of 5 hemophilia A patients who were using bypassing agents and followed-up between 2008 and 2016 in Hacettepe Hematology Department were analyzed retrospectively. All of the ethical considerations were strictly handled in accordance with the Helsinki Declaration. As a standard of care/action of the hospitals of Hacettepe Medical School, it was confirmed based on patient

records that all of the study participants gave informed consent at the time of hospitalization and relevant diagnostic/therapeutic standards of care. All data were taken from Hacettepe University Medical School Hospital database. Patient records/information was anonymized prior to analysis. Parameters of age, bleeding site, bleeding complications, inhibitor levels, medication type and duration, bleeding complications were noted. In the study patients, evaluation of response to treatment depended upon the patients' clinical condition. Physical examination was performed in every patient and depending on clinical condition X-ray or magnetic resonance imaging were performed in some patients also.

3 Results

A total of 19 bleeding episodes of 5 patients were analyzed. The median age of the patient group was 40 (28-78). All of the patients had diagnosis of hemophilia A and all patients were high responders. The median factor level was 1% (0-6%). Only one patient had mild hemophilia A, whereas other patients had severe hemophilia A. The median inhibitor level was 15.1 BU (9.3-56.0 BU). The characteristics of bleeding episodes and the treatment approaches are given in Table 1. There were 4 knee hematoma, 3 tooth extraction, 3 elbow hematoma, 2 prophylaxis, 2 major surgery, 1 psoas hematoma, 1 maxillary hematoma, 1 inguinal hematoma, 1 leg graft operation and 1 gastrointestinal bleeding episodes of hemophilia A patients with inhibitors. In 11, 5 and 3 bleeding episodes, FEIBA, recombinant factor VIIa and FEIBA + recombinant factor VIIa were given to the patients, respectively. The treatment durations differed between 1 and 14 days depending on the bleeding and clinical course of the patients. Generally the treatment with bypassing agents was successful, and only in one patient who had elbow hematoma encountered serious bleeding which was taken under control by switching the bypass agent.

4 Discussion

The preparation of hemophilia A patients with inhibitors is compelling compared to patients without inhibitors. Two decades ago, elective surgery in hemophilia A patients with inhibitors is contraindicated because of the bleeding risks. However at the present time, with the help of new bypassing agents surgical operations are performed with success. Unlike hemophilia A patients without inhibitors, the factor 8 concentrates are ineffective because of circulating antibodies in patients with inhibitors. The two main bypassing agents are recombinant factor VIIa and activated prothrombin complex concentrate (FEIBA) which also contains vitamin K dependent factors (Factor 2, 7, 9, 10). In the literature the dosing of these agents are described (Table 2) [8]. In this paper, we offer a different approach to hemophilia A patients with inhibitors who will undergo surgical operation (Table 2). Bypassing agents eliminate the need of intrinsic pathway originated "tenase" complex which activates factor X. Recombinant factor VIIa directly activates factor X whereas FEIBA provides precursors for factor X, thus both agents bypass the pathways. FEIBA is considered to be an effective bypassing agent that controls bleeding episodes [9]. However since the activated proteases that provide the pro-coagulant activity of FEIBA have short half-life, initial hemostasis could be followed by breakthrough bleeding between doses that could lead to problems in maintaining hemostasis [10]. Moreover, FEIBA comes with a risk of throm-

Table 1: The characteristics and treatment approaches of the bleeding episodes in adult hemophiliac patients with inhibitors

Clinical Condition	Number of patient	Bypassing Agents and Doses	Days of dose given
Bleeds (n:11)	3	Recombinant factor VIIa, 3-4 x 90 μg.kg^{-1}	1-3
	7	Activated prothrombin complex concentrate (FEIBA), 1-3 x 50-100 IU.kg^{-1}	1-5
	1	FEIBA, 2 x 100 IU.kg^{-1} switched to Recombinant factor VIIa, 6 x 90 μg.kg^{-1}	14
Minor Surgery (n:4)	2	Recombinant factor VIIa, 3-6 x 90 μg.kg^{-1}	3-7
	2	FEIBA, 2 x 70 IU.kg^{-1}	14
Major Surgery	2	(Our proposed protocol) First 3 days Recombinant factor VIIa, 6 x 90 μg.kg^{-1} and then FEIBA, 2 x 50 IU.kg^{-1}	14
Prophylaxis	2	FEIBA, 2 x 70 IU.kg^{-1}	2

Table 2: The preparing methods for surgery in hemophilia A patients with inhibitors

	Bypassing Agent	Pre-operative dosing	Post-operative dosing
In the literature*	Recombinant factor VIIa	Bolus 90-120 µg.kg-1	<u>0-48 hours</u>: 90 µg.kg-1/for each 2 hours, <u>3-4 days</u>: 90 µg.kg-1/for each 3 hours, <u>5-7 days</u>: 90 µg.kg-1/for each 4 hours, <u>8th day-end of treatment</u>: 90 µg.kg-1/for each 6 hours
In the literature*	Activated pro-thrombin complex concentrate	Bolus 75-100 IU.kg-1	<u>0-3 days</u>: 70 IU.kg^{-1}/for each 8 hours (for maximum dose of 200 IU.kg^{-1}/ per day). <u>4th day-end of treatment</u>: 50 IU.kg^{-1}/for each 8 hours
Our Method	Recombinant factor VIIa+ Activated pro-thrombin complex concentrate	Bolus 90 µg.kg-1	<u>In the post-operative 2, 4, 6, 8, 12, 16, 22, 30, 38, 46, 54, 62, 70 hours</u>: Recombinant factor VIIa with dose of 90 µg.kg^{-1} <u>4th day-end of treatment</u>: 2x50 IU.kg^{-1} Activated prothrombin complex concentrate (FEIBA). Treatment should stop in 7 or 14 days depending on patient's clinical condition.

*Reference number 8.

bosis that is likely to occur with large doses [11]. Another problem about FEIBA is the absence of an in vitro assay that would confirm in vivo hemostatic efficacy. Thus, the treatment answer in bleeding episodes in each patient could be different [4]. The treatment approach for each patient should be personalized and it is accepted that if there is no treatment answer for any bypassing agent the other agent should be tried [4]. In the literature the optimal dose for FEIBA treatment was given as 50 to 100 units/kg and doses above 200 units/kg is not recommended because of the risk of disseminated intravascular coagulation development [4]. The optimal dosing frequency of FEIBA is every 8 to 12 hours; more frequent dosing is associated with increased thrombotic risk [4]. The usage of FEIBA for prophylaxis is also stated in the literature [12]. In our study FEIBA was effective for controlling the bleeding episodes in hemophilia A patients with inhibitors. On the other hand, in the literature it was stated that recombinant factor VIIa has excellent treatment response in majority of hemophilia A patients with inhibitors [13]. The difference of recombinant factor VIIa from FEIBA is that tissue factor is essential for factor VIIa to be effective therefore with recombinant factor VIIa treatment coagulation occurs only at local sites of hemostasis thus avoiding the risk of systemic coagulation that could happen with FEIBA treatment [11]. In the literature, the optimal dose for recombinant factor VIIa was given as 90 to 120 mcg/kg at two- to three-hour intervals until the bleeding was controlled [4]. The usage of recombinant factor VIIa for prophylaxis is stated in the literature [14]. The efficiency of recombinant factor VIIa and FEIBA was compared in the literature; both agents had 80-90% efficacy rate and neither agent shown to be superior in efficacy [15]. The

usage of both agents together is shown to be very effective. However because of increased thrombotic risk, combination treatment is only recommended in serious life-threatening bleedings [16]. So, the risk of systemic coagulation is lower in rFVII than FEIBA. Although the bypassing agents provide a safe management of patients with inhibitors, the efficacy of these agents always remains lower than pure factor concentrates which are given to patients without inhibitors. As a result, hemophilia A patients with inhibitors have always a higher risk of bleeding than patients without inhibitors even in the presence of bypassing agents.

Another major concern about the management of hemophilia A patients with inhibitors is the cost of the treatment. Especially in the lower or middle income countries, the cost of bypassing agents is a great problem. In Turkey, the average cost for surgery preparation of a 70 kg hemophilia A patient with inhibitor is $267000, $114000 and $108000 with recombinant factor VIIa, FEIBA and our protocol, respectively. So, if there is a systemic coagulation risk generally rFVII should be preferred. The regular usage of both products at the same time is not recommended because of thrombosis risk. What we offer is to use rFVII in first 3 days and then switching to FEIBA with a different dosing protocol, which offers us a safer, cheaper and flexible control of the bleeding. We offer a different approach from the literature because of three main reasons. Firstly, in our protocol we start the treatment with recombinant factor VIIa for the first three days. The main reason for this choice is the short procoagulant half-life of bypassing agents and the need of frequent infusions to cover all hours of a day in order to quickly and safely achieve hemostasis. In our protocol we do not prefer

FEIBA in the beginning because there is a risk of thrombosis if it is used more frequently than every 8 hour and there is a limit dose of 200 units/kg/day. In our protocol after safely achieving the initial hemostasis with recombinant factor VIIa ,we prefer to continue treatment with FEIBA till 7th or 14th days after bleeding. Secondly, our protocol is adjusted to consider health economics. Cost of recombinant factor VIIa is more than twice the cost of FEIBA. Therefore we prefer to use recombinant factor VIIa in first 3 days, the time interval where the bleeding risk is maximum and the homeostasis is the primary target. After achieving the initial hemostasis we set our preference to health economics first since the bleeding risk is decreased and the less frequent doses are sufficient to stabilize the clinical course of patient. Thirdly, we extended the time interval between doses of both bypassing agents without increasing bleeding risks because the half-life of both agents enables us to modify the protocol with more flexibility. This modification let us to control the drug costs without facing extra complications or bleeding risks. To conclude, in this paper we have evaluated our clinic's data about hemophilia A patients with inhibitors and we offer a different protocol in the management of bleeding episodes for these patients.

Conflict of interest statement: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/ or affiliations relevant to the subject matter or materials included.

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