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Hemorrhage Treatment Report of Patients Suffering from Glanzmann's Thrombasthenia Resulting Hospitalization from 2006 to 2011 at Mofid Children's Hospital

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Abstract

Background: The present study evaluated treatment outcomes and the treatment indexes among Glanzmann's patients in Mofid Children's Hospital, Tehran, Iran.

Patients and Methods: A retrospective cross-sectional study was performed to evaluate the treatment protocols on 15 Glanzmann's patients with bleeding therapeutic records in Mofid Children's Hospital, Tehran, Iran, from 2006 to 2011.

Results: The total recombinant factor VIIa used was 137mg and the total infused platelet concentrates was 68 units, with platelets used in order being: apheresis platelets, leukoreduced pooled platelets, leukoreduced platelets, and random donor platelets with 35, 16, 13 and 4 units respectively. In 90% of bleeding sequences, leukoreduced platelets were available and the average admission per patient was 3.46 times, the average leukoreduced platelets consumption per patient was 4.26 units and the average use of recombinant factor VIIa per patient was 9.13mg. Other Indexes included the average hospitalization per patient per year of 0.69% times, the average consumption of non- random platelet per patient per year of 0.85% units, the average consumption of recombinant factor VIIa per patient per year of 1.83mg, the average consumption of non random platelet for any hemorrhage incidence or elective surgery of 1.3 units, and the average consumption of recombinant factor VIIa for any hemorrhage incidence of 2.8mg.

Conclusion: By extracting the consumption of therapeutical products to treat Glanzmann's thrombasthenia in our center we could estimate the future treatment needs of our medical center. More thorough investigation of patients from different age groups is recommended to achieve more reliable results.

Key Words: Glanzmann's thrombasthenia, platelet, rFVIIa, treatment index.

Introduction

Glanzmann's thrombasthenia is a rare inherited autosomal recessive bleeding disorder caused by platelet disability in binding to fibrinogen leading to defective platelet aggregation [1-5]. The underlying defect in this disease is an abnormality in the gene encoding of integrin αIIbβ3 chains of fibrinogen receptor [4-6]. The prevalence of this disease in Iran is approximately 1/200000 and the main signs are: petechiae, purpura, vaginal bleeding and nose bleeding [3]. Diagnosis is by platelet flow aggregometry and flow cytometry; in aggregometry the platelet aggregation is seen with all of the agonists expects ristocetin and in flow cytometry a decrease in CD41 and CD49 is observed [4-10]. There is no correlation between bleeding (frequency, severity and site) with subgroups of Glanzmann's thrombasthenia phenotypes [4-5]. There is evidence that other factors such as genetic and inherited thrombophilia have an important role in bleeding severity among Glanzmann's thrombasthenia patients [4-5]. There is no specific treatment for the disease, but platelet transfusions

and recombinant factor VIIa (rFVIIa) administration may be used in patients who show severe bleeding [1-10]. Glanzmann's thrombasthenia is a life-long condition for which there is no cure [8-15] and patients should take precautions to avoid bleeding [10-17]. Treatment approach in Glanzmann's are: preventional procedures such as: mouth and teeth's hygiene, not using NSAIDs such as aspirin, and other anticoagulants or antiplatelet agents. Bleeding treatment consist of local procedures like antifibrinolytics and local haemostatic agents (regenerated oxidized cellulose bandages, chitosan based powders and bandages, artificial cianoacrylic adhesives etc.), hormonal therapy in females, and finally the use of platelets and active recombinant factor VIIa [11-25]. To prevent platelets resistance it would be better to use leukoreduced and preferably apheresis platelets [2]. Some difficulties of the mentioned treatments are the high price and the low availability of rFVIIa and also high price of platelet filters and apheresis methods [9, 22, 24]. Regarding the variety of the mentioned treatment methods and difference in availability of any of these treatment factors in various therapeutic centers, there is not any well known guideline to treat moderate to severe outpatient bleedings and readiness for elective or emergency surgeries [11]. This unevenness of therapeutic methods has led to the need for indexes to evaluate the success of any of the methods and the used materials and the subsequent prediction of medicines in need in every center [1,8,21,25]. Therefore in this retrospective study we aimed to extract the therapeutic program results of our center to define the needed treatment indexes, which provide the data for a better treatment plan.

Patients and Methods

In this retrospective, descriptive-analytical and cross-sectional study all Glanzmann's thrombasthenia patients from 2006 to 2011 who were admitted to the Mofid Children's Hospital, Tehran, Iran for controlling their bleeding or for surgery procedures were evaluated. Individual specifics, examination procedures, bleeding events, and the type and amount of consumed therapeutic factors were extracted from the patients' records. In mild to moderate bleeding which did not respond to local procedures such as antifibrinolytics and local haemostatic agents (regenerated oxidized cellulose bandages, chitosan based powders and bandages, artificial cyanoacrylic adhesives etc.) within the first 24 to 48 hours, at first leukoreduced platelets (preferably apheresis platelet (ADPC) and if not available in order, leukoreduced pooled platelet (LR-PPC) and leukoreduced platelet (LR-RDPC) were used. If after 48 to 72 hours from the platelet infusion the bleeding still continued 90 micro gr/Kg of active recombinant factor VIIa, every 2 to 4 hours, for up to 270 micro gr/Kg was used (Figure 1). In severe bleedings and immediate surgery procedures to speed the treatment results using all of the mentioned procedures might become a necessity.

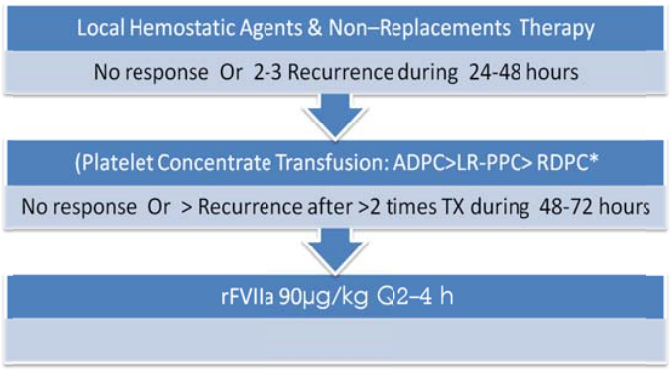

Figure 1: Therapeutic levels for mild to moderate bleeding.
Therapeutic levels of mild to moderate bleeding depending on therapeutic products availability and their response.

According to extracted data from records, patients raw therapeutic characteristics including times of bleeding events in each patient, bleeding events responding to each of the therapeutic factors, bleeding events resistant to each of the therapeutic factors, responding or resistance to each of the therapeutic factors, numbers and percentage of replacing the therapeutic factors due to unavailability of each of them were recorded. Finally the required indexes were achieved using this information.

Results

The evaluated patients in the study were 15 individuals within 2 to 14 years old range (average 3. 5 years old) and the ratio of males to females was 5 to 1. From 52 treatment episodes, 38 were bleeding incidents, 11 were hospitalizations for elective surgery and 3 were dismissed due to no bleeding. From the total bleeding events in order, 19 cases (50%) were only treated with platelets, 6 cases (16%) with rFVIIa and 13 cases (34%) controlled by receiving both products. In 11 elective hospitalized cases in order, 8 cases were treated with platelets, and 3 cases were controlled by receiving both products. Out of 15 patients, 4 of them only received platelets and the rest received rFVIIa (only 2 patients due to platelet resistance and the others due to unavailability of leukoreduced platelets). Two out of 11 patients receiving rFVIIa showed resistance to rFVIIa (Table 2), the total consumed rFVIIa was 137mg and the platelet units used were 68 units. Finally, the index of consumed rFVIIa per year was 27.4 mg and the consumed platelets units per year were 13.6 units. All of the consumed platelets were leukoreduced expect that in 4 occasions (3 patients) random platelets were used and it was due to temporarily unavailability of platelet leukocyte filter, leukoreduced pooled platelet and apheresis.

The important findings extracted from our data are as follow: the average bleeding injury leading to hospitalization or elective surgery per each patient per year: 0. 69 times, the average non random platelet units used for each patient per year 0. 85 units, the average rFVIIa consumption for each patient per year: 1.83mg, the average non random platelet consumption for every bleeding incidence or elective surgery: 1.3 units, the average rFVIIa consumption for every bleeding incidence: 2.8mg.

Discussion

Glanzmann's thrombasthenia is a rare bleeding disorder with no specific treatment guideline[4-12]. In Glanzmann's disease different therapeutic procedures in order to control bleeding include: local haemostatic agents (in moderate to severe bleedings), platelet (apheresis or pooled and in case of unavailability usage of random donor platelet) and rFVIIa. It should be kept in mind that by using platelet (especially if not leukoreduced) platelet resistant from alloimmunization might increase. Also it should be considered that rFVIIa, has a success rate of near 90% in stopping the bleeding according to literature [1,3,6,8,15,21,25]. In a study by Poon et al. 24 patients with acute bleeding (therapeutic) and 4 patients with hernia surgery (prevention) received rFVIIa with anti fibrinolytic

Table 2: The therapeutic methods used to treat Glanzmann's patients during the study's period.

	Number	Only Platelet	Only rFVIIa	Both (Platelet and rFVIIa)
Patients number	15	4	-	11
Bleeding Incidence	38	19	6	13
Elective surgery	11	8	3	-
Resistance to platelet	2	-	-	2
Resistance to rFVIIa	2	-	-	2

and in all patients the bleeding stopped expect for one patient who following not responding to rFVIIa received platelets [6]. This article points to rFVIIa as a good substitute for platelets 6. In our study only two patients did not full respond to rFVIIa and needed platelets transfusion. Chuansumrit et al. used rFVIIa and local agents to stop the bleeding in 4 patients while receiving surgery with success[7]; which is similar to our findings showing most patients respond to rFVIIa. rFVIIa may enhance the expression of endothelial deposition of GP IIb-IIIa–deficient platelets, thus antifibrinolytic therapy, plus rFVIIa improves the clot formation [25-27]. There are some reports which have claimed severe menstruation hemorrhage with rFVIIa [7,9,14,16,19]. Most of our patients were in pediatric age range and menstruation was not the main problem our female patients. Bierling et al., have demonstrated that in Glanzmann's disease alloimmunization upon GpIIb and GpIIIa rarely develops but also conclude that it usually appears in patients which repetitively receive transfusion [11]. They suggested that patients receive the leukoreduced blood products [11]. Our study showed only two patients with resistance to platelets transfusion. It should be mentioned that therapeutic decisions in different centers are different and this has several reasons including: blood products availability (leukoreduced Platelet, apheresis platelet), cost: rFVIIa products are very expensive in comparison to blood products, histories of insufficient respond to rFVIIa, age: in adults with the history of previous random platelet therapy, alloimmunization risk is higher, no accessible specific therapeutic protocol in most centers [11-21]. Refractory bleeding in Glanzmann's patients requires the transfusion of human leukocyte antigen (HLA)–matched platelets to prevent alloimmunization [8, 17]. Some centers recommend HLA-matched sibling allogeneic stem cell transplantation (SCT). It has been successfully performed in patients with Glanzmann's thrombasthenia and platelet alloimmunization but it is not recommended in most patients due to its complications [1, 19,26]. A platelet transfusion is necessary before invasive procedures (surgical or dental). Another challenge for Glanzmann's patients is pregnancy. HLA-matched platelet transfusions with rFVIIa are essential before delivery and at least one week postpartum [25-27]. We did not have any patients with pregnancy. Thrombosis has been reported in less than 1% of patients receiving rFVIIa [28-29], but we did not have any thrombotic complications. The absence of therapeutic algorithms for Glanzmann's patients leads difficulties in therapeutic planning to predict the therapeutic needs in centers level and also in the country level [13, 21].

Conclusion

By extracting the consumption of therapeutical products to treat Glanzmann's thrombasthenia in our center we could estimate the future treatment needs of our center. More thorough investigation of patients from different age groups is recommended to achieve more reliable results.

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