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CASE REPORT

Perioperative administration of recombinant activated factor VII in a Glanzmann's thrombasthenia patient with platelet refractoriness: case report

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Abstract Glanzmann's Trombasthenia (GT) is a genetic disorder, that develops with a tendency toward bleeding and is characterized by the absence or decrease in platelet aggregation. Surgical bleeding may be difficult to control. Platelet transfusion is the main treatment, albeit refractoriness can occur. We describe the case of a patient with GTand platelet refractoriness, who was submitted to radical prostatectomy and dental extraction. The perioperative treatment with apheresis platelet concentrate and activated recombinant factor seven allowed the procedures to be performed uneventfully. We discuss the complexity of the case and the treatment option.
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Introduction

Glanzmann's Thrombasthenia (GT) is a rare autosomal recessive hemorrhagic disorder (1:1,000,000), characterized by the absence or decrease of platelet aggregation, with normal platelet count and morphology. It was first described by a Swiss pediatrician, Edward Glanzmann in 1918, as a "Hemorrhagic Hereditary Thrombasthenia".[1] Platelet dysfunction is caused by quantitative and/or qualitative defects in platelet integrins αIIbβ3 (formerly known as Gycoprotein [GP] — IIb-/IIIa), which are receptors on the surface of platelets that mediate the final step of platelet aggregation.[1,2] Clinically, GT develops with a tendency toward mucocutaneous bleeding throughout life. Post-trauma and post-operative bleeding can be remarkably severe. No specific treatment is available. Platelet transfusion is a beneficial measure, but in many patients, its effectiveness is reduced by the development of alloimmunization that can occur after recurrent transfusions,[1,2] thus the use of recombinant activated factor VII (rFVIIa) becomes a feasible

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alternative. This case report describes the perioperative management of a patient with GT who underwent surgical procedures with potential risk of hemorrhage. The present report is relevant because GT is a rare disorder with scarce perioperative management data available and it poses difficulty in conducting randomized clinical trials.

Case report

A 62-year-old male patient, 85 kg, diagnosed with GT in childhood, was scheduled for open radical prostatectomy and surgical tooth extraction. At the time of GT diagnosis, the patient referred frequent episodes of epistaxis and the condition progressed to gingival bleeding and chronic anemia. Regarding family history, the patient referred two sisters with diagnosis of GT. In his past anesthetic history, at 12-years of age he underwent surgical repair of a knee fracture that required blood transfusions. Three months before the current presentation, he underwent a prostate biopsy complicated with hemorrhagic shock, although preoperatively he received platelet transfusion. He was taking tranexamic acid. Laboratory tests showed normal red blood cell count, 176 $\times$ 103 mm^{-3} platelets and normal blood clotting tests. Optimization for the scheduled surgeries was performed by the hematologist and consisted of the administration of one unit of apheresis platelets and rFVIIa at a dosage of 350 KUI (82.0 $\mu g.kg^{-1}$), both one hour before surgery. Intraoperatively the same dosage of rFVIIa was administered every two hours. Monitoring consisted of pulse oximetry, ECG tracing, capnography, and invasive blood pressure after radial artery cannulation. Balanced general anesthesia was performed, using sevoflurane inhalation combined with target-controlled infusion of remifentanil. The duration of the surgical procedures was 4 hours, with estimated blood loss of approximately 500 mL. The procedure was uneventful, and the patient was extubated and sent to the ICU. He received platelet concentrate every 12 hours for 6 days and rFVIIa (350 KUI) every 3 hours on the first postoperative day (PO), then every 4 hours on the second PO, every 6 hours on the third PO, every 8 hours on the fourth PO, and every 12 hours on the fifth PO, followed by tranexamic acid until hospital discharge, on the seventh PO. The patient presented hematuria, anemia, and platelet transfusion reaction as postoperative complications.

Discussion

The case illustrates the management for preventing hemorrhagic complications in surgical patients with GT. Prophylactic or therapeutic platelet transfusion is the standard perioperative treatment for patients with GT. However, repeated transfusions can elicit alloimmunization to Human Leukocyte Antigens (HLA) and/or to GP IIb and IIIa, causing platelet transfusion refractoriness and future transfusions ineffective. This occurred for the patient described here and was evident in the prostate biopsy procedure, which was complicated with hemorrhagic shock, as he showed refractoriness to prophylactic platelet transfusion. Thus, rFVIIa represents an alternative for bleeding prevention and treatment during surgery or other invasive procedures. Some studies suggest that rFVIIa can be effective, with no safety concern for patients with GT showing platelet antibodies and/or platelet refractoriness and would be the most effective alternative.[2] The case reported enabled us to perform two procedures with high risk of hemorrhage, such as radical prostatectomy and surgical tooth extraction. GT is the most frequent hereditary disorder of the platelet αIIbβ3 integrin receptor complex. When there is platelet activation, αIIbβ3 shows an inside out response to signaling and shifts its configuration from resting to the active state, that is required for the binding of fibrinogen and other ligand proteins.[1,2] Although rare, GT has a worldwide distribution. The first manifestations are in childhood, rarely in adolescence. The analysis of a registry of 187 patients with GT, shows that in 85% of the patients the disorder started before 14 years of age, and the mean onset age was 5.6 years.[2] Bleeding is mainly mucocutaneous in nature with hematomas, petechiae and bruises after minimal trauma. Some patients have only small hematomas, others often show potentially fatal hemorrhages. Gingival bleeding and epistaxis are frequent and can be difficult to control with local measures and require transfusions. Menorrhagia occurs in almost all girls, and child delivery is associated with risk of severe or even fatal hemorrhage.

Although, by definition, all patients with GT have complete absence of platelet aggregation, the underlying biochemical abnormality varies from one relative to another. As a result of these differences, GT is classified into 3 types according to the levels of αIIbβ3 protein on the platelet surface. Approximately 75% of GT patients are classified as type 1 (0—5% of αIIbβ3); type II (5—20% of αIIbβ3) occurs in 15% of patients; and around 10% of patients are classified as type III (variant type, above 20% of αIIbβ3).[2] The diagnosis of GT is often overlooked, since GT has clinical and laboratory features in common with other platelet disorders. Ordering appropriate laboratory tests is essential. Normal platelet count values do not rule out GT, as generally the test shows values within normal range in patients with GT. Complete blood count may reveal iron deficiency. Prothrombin time and activated partial thromboplastin are normal. However, bleeding time will be prolonged, although it is not recommended as a diagnostic tool, due to lack of standardization, trauma associated to the test and low positive predictive value. There are multiple more specific and dedicated laboratory tests, such as light transmission aggregometry, the gold standard for diagnosing platelet function;[3] Platelet Function Analyzer (PFA), a highly sensitive test for diagnosing GT; flow cytometry and molecular analysis of the ITG2B and ITGB3 genes.[1] The rarity of GT makes it difficult to carry out controlled clinical trials. Thus, case reports enable acknowledging the best options for the management of these patients. Therapeutic options for treating bleeding in patients with GT are very limited. Bleeding episodes can be treated with local measures and antifibrinolytics. Platelet transfusion is the standard of care if bleeding can be controlled with these conservative measures. It is also the standard prophylaxis in surgical patients, but it is estimated that nearly 50% of patients develop antiplatelet antibodies,[2] resulting in accelerated platelet destruction and transfusion failure. To mitigate these risks, ideally single-donor platelets with compatible Leukocyte Antigen (HLA) and apheresis platelets with reduced leukocytes should be used, as was performed in this case. rFVIIa represents a viable alternative to overcome the platelet refractoriness issue. The exact hemostatic mechanism of rFVIIa is unclear. rFVIIa is known to play a fundamental role in

the coagulation cascade starting the process. Hemostatic doses of rFVIIa seem to bind to the surface of activated platelets and thus increase local thrombin generation and adhesion of GP IIb and IIIa deficient platelets. With enough thrombin formation, there is the creation of a hemostatic plug of stable fibrin.[1,2] Duman et al.[4] showed a case of a child with GT who had bleeding during an adenoidectomy and was satisfactorily treated with rFVIIa. Conversely to the present case, rFVIIa was used for treatment and not for prophylaxis of hemorrhagic events. A study by Poon[5] analyzing rFVIIa efficacy in patients with GT, with or without platelet refractoriness, submitted to surgery or not, reported the use of a mean dose of 80 μg.kg^{-1}, at 2-hour intervals for bleeding episodes and surgical procedures. Although there is a difference in the management related to the extension of the surgery, rFVIIa is indicated for both minor and major procedures, as reported in the present case. In the postoperative period, the frequency of administration is decreased as adequate hemostasis is attained, and antifibrinolytic administration can be started. The association of antifibrinolytic with rFVIIa should be avoided because of the risk of thrombosis. Dental procedures present a risk to patients with GT, and often must be done in a hospital setting. In the case here reported, performing the prostatectomy and the dental extraction during the same procedure proved to be understandable due to the risk and high cost of carrying out each procedure separately. Administration of rFVIIa is associated with potential risks of thromboembolic events and allergic reactions, therefore, care must be taken to comply with administration guidelines.

Conclusion

GT is a rare disease and can present a major challenge during the management of invasive or surgical procedures, due to scarce expertise on the disease or the lack of adequate preparation of the patient. The management plan by the surgical team together with the hematologist is crucial to prevent potentially fatal complications. In the case presented, the administration of rFVIIa as a hemostatic alternative therapy was considered effective and with an appropriate safety profile.

Informed consent

Written informed consent for publication of this article was obtained from the patient.

Conflicts of interest

The authors declare no conflicts of interest.

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