

## Case Report

# Transient Ischemic Attack in a Hemophilia Patient with Severe Preeclampsia after Preoperative Administration of Tranexamic Acid and Factor VIII Replacement for Cesarean Section

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**\*Corresponding author:** Hoffman CH, Department of Anesthesiology, Thomas Jefferson University Hospital, 111 S. 11<sup>th</sup> Street, Suite 8290 Gibbon, Philadelphia, PA 19107, USA**Received:** April 08, 2021; **Accepted:** May 07, 2021;**Published:** May 14, 2021**Abstract**

Hemophilia A in females accounts for few cases due to hemophilia A and B having X-linked recessive inheritance patterns. Hemostatic changes in pregnancy include an increase in coagulation factors and von Willebrand activity, placing hemophilia patients at an increased risk for Postpartum Hemorrhage (PPH). General recommendations include considering pharmacologic prophylaxis, including tranexamic acid and factor replacement when necessary. The ultimate goal is to prevent uncontrolled bleeding during vaginal or operative delivery. Benefits of prophylactic therapies must be weighed with relevant risk profiles of each intervention. We present a case where a parturient with hemophilia prophylactically treated with TXA and FVIII experienced a transient ischemic attack. We discuss the background information known regarding tranexamic acid and factor replacement, and the subsequent recommendations for their use in this patient population. We consider recommendations to expand the multidisciplinary team incorporated in the assessment and planning for the peripartum care of such a patient.

**Keywords:** Tranexamic acid; Factor VIII replacement; Hemophilia; Transient ischemic attack; Preeclampsia; Hemostatic changes in pregnancy

**Introduction**

Hemophilia A in females accounts for 2.89% of prevalent cases [1]. This rarity is attributed to hemophilia A and B having X-linked recessive inheritance patterns. Females that are carriers for the disorder have a range of active Factor VIII, resulting from random inactivation of one X chromosome [2]. Depending on the level of active factor level, the patient is more at risk for major bleeding complications, especially in the postpartum and postoperative period. The disease prevalence overall is just 1/10,000 births, making it hard to study. Thus, information and recommendations in the management of females with hemophilia A during pregnancy warrants attention.

Hemostatic changes in pregnancy include an increase in coagulation factors VII, VIII, X, XII, von Willebrand antigen, and von Willebrand activity [1,2]. Attenuated rise in FVIII during the second trimester of pregnancy is what places hemophilia patients at an increased risk for Postpartum Hemorrhage (PPH). The recommended level to increase factor VIII *via* replacement therapy to prevent PPH is the same as what is acceptable for placement of regional anesthesia (above 50 IU dL<sup>-1</sup>) [3]. There have been no reported neurological complications from regional anesthesia after factors were prophylactically given [2]. Given its safety profile, spinal anesthesia is the preferred choice for this parturient undergoing cesarean section.

During trauma there is early activation of fibrinolysis causing increased bleeding and mortality. This same activation happens

during childbirth, with serum tissue plasminogen activator concentration doubling 1 hour post-partum [3]. Tranexamic Acid (TXA) reduces bleeding in these settings by inhibiting the enzymatic breakdown of fibrinogen and fibrin by plasmin. Its role in the perioperative environment outside of trauma settings is increasing and often studied.

The highest chance for stroke in the parturient is in the peripartum and postpartum period, affecting 30 out of 100,000 pregnancies [4]. This is 3 times the risk in non-pregnant patients in the same age group. This risk increases by up to 5-6 times in parturients with preeclampsia [5,6]. Preeclampsia complicates 3 to 8% of all pregnancies [4]. The disease is characterized by widespread endothelial cell dysfunction, immune dysregulation, and blood-brain barrier disruption, all contributing to increased cerebrovascular risk. The risk factors for developing this disease during pregnancy include nulliparity, obesity, pregestational diabetes, thrombophilia, and pre existing hypertension or renal disease [2,5].

We present a case where a parturient with hemophilia prophylactically treated with TXA and FVIII experienced a transient ischemic attack. We discuss risks, benefits, and recommendations of prophylactic agents for this patient population.

**Case Presentation**

A 35 year old female G4P3 with di-di twins presented for cesarean section in the setting of severe preeclampsia with severe features. Worsening shortness of breath and chest radiography showing

pulmonary edema necessitated supplemental oxygen and diuresis. Her medical history included 3 unremarkable vaginal deliveries, anemia, and hemophilia A. Prior to the procedure the patient received factor VIII replacement and perioperative tranexamic acid per hematology recommendation to decrease intraoperative bleeding. Cesarean section was performed under spinal anesthesia without complication. In the immediate postoperative period the patient developed expressive aphasia. She was admitted to the neuro ICU where the decision was made to not administer TPA and to proceed with further work up. Head CT and later brain MRI did not show acute infarction or hemorrhage. Aphasia resolved on postoperative day 2 and the etiology was believed to be a transient ischemic attack. Patient was discharged on postoperative day 7 to home without any neurological deficits.

## Discussion

Tranexamic acid use on obstetrical floors is used prophylactically to prevent PPH (defined as >1000 mL of blood loss), the number one cause of death for the pregnant population [3]. TXA use in surgery has been shown to reduce blood loss and surgical deaths due to bleeding by a third [3]. Of note this trial did not show any increase in vaso-occlusive events compared to the placebo group [3]. Pre-incision TXA use has also increased for cesarean sections. Randomized control trials show significantly decreased mean blood loss, severe PPH, and need for additional uterotronics besides oxytocin [7]. No statistically increased adverse events including thromboembolism were reported [7].

Given our patient presented for twin delivery *via* cesarean section in the setting of anemia and hemophilia, she was at higher risk for adverse outcomes from significant PPH. The patient in our case was given TXA prior to surgical incision to mitigate risk. A multidisciplinary team discussion included anesthesiology, obstetrics, and hematology, all coming to the same conclusion regarding TXA administration. The current recommendations per the WHO are for the early use of intravenous TXA within 3 hours of birth or as early as possible after diagnosis of PPH is made. This treatment should be added to the standard of care for patients with PPH, not a replacement for other therapies. Recommended dosing is 1 g in 10 mL at 1 mL per minute intravenously, and the option for a second dose of 1 g IV for persistent bleeding after 30 minutes [8]. The patient in our case report had these recommendations followed, as she was given this dose within 3 hours of birth.

The lack of inherent factor VIII activity or the increased factor needed to combat increased bleeding in the postpartum period places hemophiliacs at increased risk. This was shown during a retrospective study of obstetrical outcomes in patients with both hemophilia A or B. Primary PPH (500 mL of blood loss, 1000 mL for severe, within 24 hours) incidence in hemophilia A was 22% compared to 8% in the general population. Secondary PPH (excessive bleeding between 24 hours and 6 weeks of delivery) incidence was 11% compared to 0.8% in the general population [1].

Factor VIII can be given as a replacement therapy intravenously for patients with hemophilia A. The goal of treatment is to raise the factor VIII level to above 50 IU dL<sup>-1</sup> [1]. The multidisciplinary team, which included a consult to hematology, agreed factor replacement was warranted. Our patient was given factor VIII replacement,

this was given as a one time dose on the labor and delivery floor, which occurred prior to the regional anesthetic and the start of the procedure. This prophylaxis aimed to prevent potential severe PPH as well as provide safe conditions for spinal anesthetic placement with less hematoma risk. The commonly cited complications of regional anesthesia (inadequate anesthesia/analgesia, bloody tap, hypotension, dural puncture) in the patient population receiving replacement therapy did not differ from the general population [1]. Our institution's laboratory ran the factor VIII activity level rather than a quantitative value. These values range for a target value of 50-150 % activity level. Prior to pregnancy the patient's activity level was 84%. The patient's defect being a qualitative defect led to the decision for the hematology team to recommend replacement prior to surgery. Preprocedural levels after administration of replacement was 330%. The level check on postoperative day number 1 was 373%. These increased levels were likely secondary to the hemostatic changes of pregnancy [9]. Females who are carriers of the hemophilia gene during pregnancy will have Factor VIII levels that rise [5]. This is likely what contributes the increase in factor VIII activity level from the patient's pre-pregnancy labs to her peripartum and preoperative lab value.

Our patient presented with a transient ischemic attack in the immediate postpartum period. The patient had risk factors for perioperative stroke given her current preeclampsia, which increased her risk up to 5-6 times [6]. This risk is well known in the preeclamptic population as the current AHA guidelines (level A, class I evidence) recommend low dose aspirin starting at the 12th week of gestation to help reduce this risk [10]. It has been shown in lab models that the use of both TXA and factor VIII in combination produces a significant increase in clot stability [11]. The blood barrier becomes more permeable when exposed to the blood of patients with preeclampsia [11]. It is possible that this increased permeability led to increased entrance of the pro-coagulation factors given (Factor VIII replacement) and the clot stabilizing drug (TXA). This increased presence of both of these substances may have led to the increased probability of an intracerebral thrombotic event.

Perioperative physicians taking care of obstetrical patients during cesarean sections should have expanded knowledge of these conditions as it relates to stroke risk. The patient was given preoperative TXA and factor replacement to prevent the devastating effects of potential PPH. The decision affected the type of anesthetic that could be given, the potential surgical complications of bleeding, and the risk of neurological complications for stroke. This decision was made in a multidisciplinary fashion. We believe the team should have included a physician from the neurological service, which would have helped to inform the patient of the increased stroke risk and helped plan for postoperative management. Ideally, the team would meet prior to the patient's admission to discuss the case and optimal management of the patient, in a multidisciplinary care meeting.

## Consent

Consent was contained in person by the author of this case report, which is held in the electronic medical record.

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