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Tranexamic Acid-Induced Seizures in Parturient Patient during Sectio Caesarean: Case Report

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Abstract---*Introduction: Tranexamic acid has found extensive application in obstetrics to prevent and treat postpartum hemorrhage (PPH). This case report investigated an infrequent incidence in which seizures were caused by the administration of tranexamic acid. Even though tranexamic acid is generally regarded as safe, it has been associated with the infrequent yet serious side effects of tranexamic acid-induced seizures. This case report was aimed at investigating the infrequent incidence of tranexamic acid-induced seizures in postpartum patients. Case: It was reported that a woman who was 40 weeks pregnant suffered from postpartum seizures after delivery via cesarean section. These seizures occurred after tranexamic acid was administered to treat postpartum hemorrhage (PPH) caused by uterine rupture, which was accompanied by hypocalcemia. Despite not having a history of epilepsy, preeclampsia, or hypertension, the electrocardiogram (EKG) showed a prolongation of the QT interval. A comprehensive diagnostic evaluation, which involved a CT scan of the head and a D-dimer examination, was conducted, revealing no abnormalities. Discussion: Tranexamic acid, a synthetic derivative of lysine, acts as a competitive inhibitor of plasminogen activation, thereby inhibiting the breakdown of fibrin clots. Even though the exact mechanism is still being studied, some theories suggest that tranexamic acid may have a direct excitatory effect on the central nervous system (CNS) by interfering with the neurotransmitter gamma-aminobutyric acid (GABA). Conclusion: Tranexamic acid has the potential to induce seizures, even in patients without any predisposing factors. It is important for doctors to be aware of the infrequent yet serious side effects associated with tranexamic acid and should closely monitor patients, particularly during the postpartum period following a cesarean section.*
Keywords---*hypocalcemia, pregnancy, seizures, tranexamic acid.*

Introduction

Tranexamic acid has found extensive application in obstetrics to prevent and treat postpartum hemorrhage (PPH). The administration of tranexamic acid significantly reduces blood loss and the need for transfusions (Shakur-Still et al., 2023). Although tranexamic acid is generally regarded as safe, it has been associated with the infrequent yet serious side effects of tranexamic acid-induced seizures (Lecker et al., 2016).

To minimize neurological sequelae in this vulnerable population, it is imperative to implement early detection and prompt intervention. This case reports detailed the incidence of seizures in a postpartum woman following the administration of tranexamic acid to treat postpartum hemorrhage (PPH) caused by uterine rupture. In this case report, the clinical presentation and possible mechanisms were also discussed. Moreover, this case emphasized the importance of maintaining a high index of suspicion for tranexamic acid-induced seizures in the postpartum setting. This case report was aimed at investigating the infrequent incidence of tranexamic acid-induced seizures in

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postpartum patients, emphasizing the importance of awareness and monitoring of this potential complication (Hart & Sibai, 2013; Aya et al., 2016).

Case report

A 26-year-old nulliparous woman who was 40 weeks pregnant was referred to the hospital for sectio caesarea (SC) surgery due to indications of uterine rupture. In previous pregnancies, there was no history of pre-eclampsia, nor was there a history of hypertension before or during pregnancy (Kurniati et al., 2022). Additionally, the patient's vital signs were within the normal range, as indicated by the following test results: hemoglobin (Hb) level of 11.8 g/dL, hematocrit (Ht) level of 36.4%, leukocyte count of 9010/uL, and platelet count of 165,000 uL. Moreover, the current blood sugar was 65 mg/dL, urea was 17 mg/dL, creatinine was 0.78 mg/dL, sodium was 137 mmol/L, potassium was 4.9 mmol/L, calcium was 8.4 mg/dL, chloride was 107 mmol/L, SGOT was 26 IU/L, and SGPT was 12 IU/L. The coagulation examination showed prothrombin time (PT) and activated partial thromboplastin time (APTT) of 12.7–33.5 seconds. Based on the urinalysis results, it was determined that the bacteria were negative for leukocytes 0-1/LPB, negative for nitrites, and negative for protein. In addition, electrocardiography (EKG) shows bradycardia with prolongation of the QT interval.

The patient underwent regional anesthesia in a sitting position, punctured between L3 and L4 using Quincke type needle no. 25, with local anesthesia using 7.5 mg 0.5% bupivacaine heavy and adjuvant fentanyl 25 mcg. As the surgery progressed, the patient was given oxygen through a nasal cannula at a rate of 2 liters per minute (lpm), 20 IU of oxytocin intravenously (IV), 1 gram of tranexamic acid dissolved in 300 cc of ringer lactate intravenously (IV), analgesics with 1 gram of paracetamol intravenously (IV), and 30 mg of ketorolac intravenously (IV). Furthermore, bleeding during surgery was 400 cc, and urine production was 250 cc. In addition, the surgery has a duration of 65 minutes, while the administration of anesthesia lasts for 75 minutes.

Subsequently, the patient suffered a seizure episode within five minutes of receiving tranexamic acid during the surgery. Moreover, the patient experienced a tonic-clonic seizure for 3 minutes, was then administered 3 mg of midazolam intravenously, and received an oxygen face mask at 12 L/min. The patient experienced a second seizure, lasting for 2 minutes, while under observation in the recovery room (RR). The patient then received a second dose of 3 mg of midazolam and subsequently resumed treatment in the intensive care unit (ICU).

The patient was intensively observed in the intensive care unit (ICU) after the surgery. As part of the recovery process, a computed tomography scan (CT scan) of the head was performed. The results of the scan indicated the absence of any infarction, bleeding, or intracranial space-occupying lesion (SOL) (Figure 1). There were no symptoms or signs of a neurological deficit. The results of the D-dimer examination were within normal limits, further eliminating the possibility of thromboembolic events.

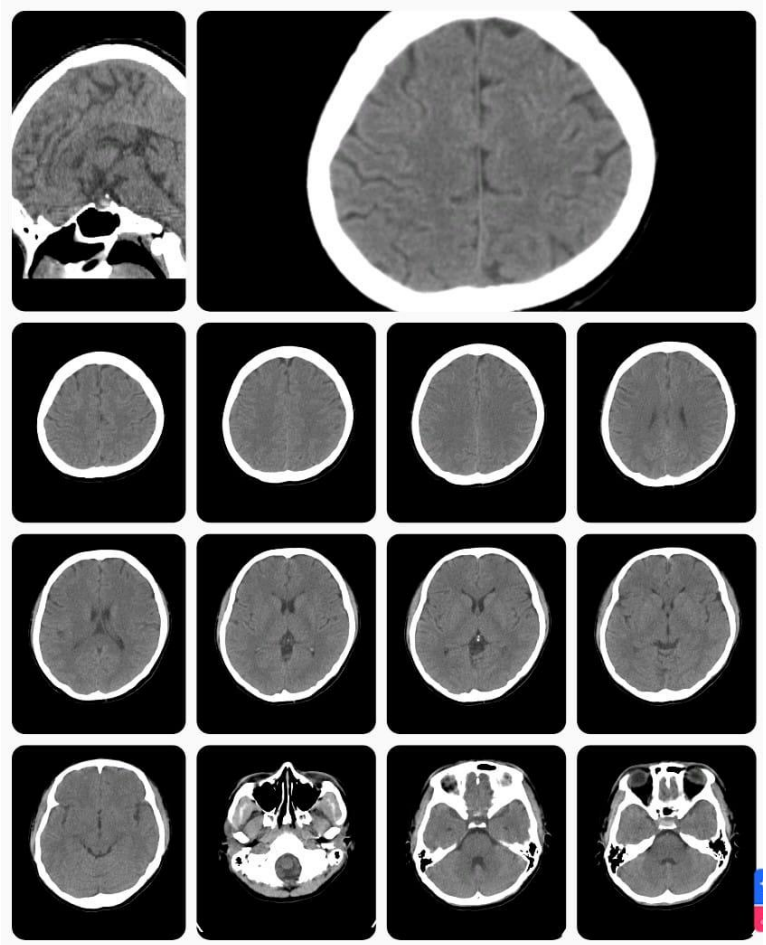

Figure 1. A CT-Scan examination of the head revealed no presence of any intracranial SOL or signs of increased intracranial pressure (ICP)

The patient was in a bradycardia condition but reported no chest pain and maintained stable hemodynamics throughout the monitoring process. Every 12 hours, the patient received 2 mg of salbutamol tablets from the cardiologist.

Discussion

The introduction of tranexamic acid marked a significant change in the management of bleeding, particularly in cases of PPH. Tranexamic acid, a synthetic derivative of lysine, acts as a competitive inhibitor of plasminogen activation, thereby inhibiting the breakdown of fibrin clots (Novikova et al., 2015).

This mechanism has proven to be effective in minimizing blood loss and reducing the necessity for transfusions, resulting in improved maternal outcomes (Novikova et al., 2015; Simonazzi et al., 2016). Multiple studies, both randomized controlled trials and observational, have consistently shown that tranexamic acid is effective in reducing the risk of severe postpartum hemorrhage and its associated complications (Shakur-Still et al., 2023; Simonazzi et al., 2016; Maged et al., 2015).

Calcium plays a crucial role in platelet function, intrinsic and extrinsic coagulation pathways, and cardiac contractility. A decrease in basal calcium levels, such as from significant blood loss caused by a traumatic injury, can lead to decreased heart function, abnormal muscle activity, and coagulation disorders (Bell et al., 2023; Bharath et al., 2011). The patient's blood tests revealed low levels of serum calcium. Therefore, the decision was made to administer tranexamic acid to the patient. Even though tranexamic acid has proven to be beneficial in managing postpartum hemorrhage, recent research indicates a potential association with seizures, particularly when administered in high doses (Lecker et al., 2016; Luo et al., 2023).

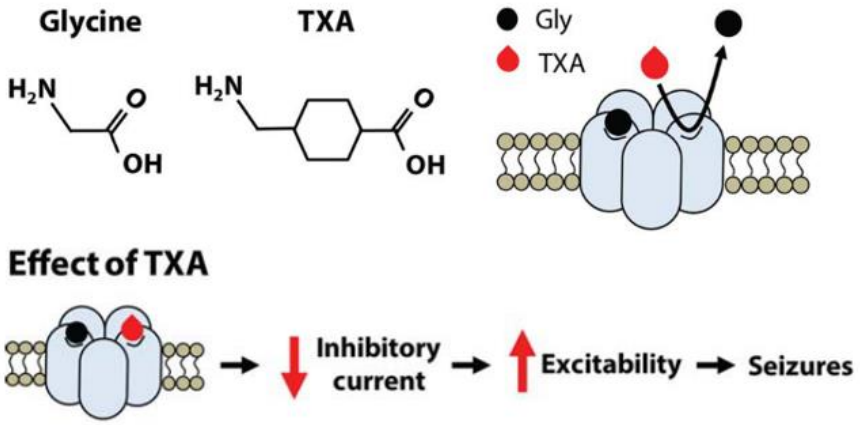

Figure 2. Tranexamic acid is a competitive antagonist of glycine receptor (GlyR). Glycine and TXA are structural analogues, so there is a decrease in anion conduction, which increases excitability and causes seizures (Taeuber et al., 2021).

Several theories have been proposed, although the exact mechanism is still under investigation. One potential explanation suggests that tranexamic acid may have a direct excitatory effect on the central nervous system (CNS) by interfering with the neurotransmitter gamma-aminobutyric acid (GABA) (Lecker et al., 2016; Lin & Xiaoyi, 2016). GABA is a major inhibitory neurotransmitter, and its antagonism may lead to neuronal hyperexcitability, which can ultimately lead to seizures.

Another theory proposes that tranexamic acid indirectly contributes to seizures by altering cerebral blood flow. The antifibrinolytic properties of tranexamic acid may increase the risk of thromboembolic events, which can potentially cause cerebral ischemia and subsequent seizure activity (Figure 1) (Taeuber et al., 2021). In addition to pre-existing medical conditions or concomitant medications that cause the patient to experience seizures, the use of tranexamic acid can have a combined effect that increases the risk of experiencing this complication (Kawagishi et al., 2022).

Although seizures induced by tranexamic acid appear to be relatively low, ranging from 0.9% to 2.5% in non-pregnant women (Lecker et al., 2016), it is important to note that the extensive use of tranexamic acid in obstetrics means that a large number of women may still be affected. The clinical presentation of seizures caused by tranexamic acid can vary, including generalized tonic-clonic seizures, focal seizures, or even altered mental status without excessive motor activity (Lecker et al., 2016; Kawagishi et al., 2022). The inherent variability in these presentations emphasizes the importance of maintaining a high level of suspicion, particularly during the postpartum period, as seizures can be caused by a variety of factors.

It is critical to promptly recognize and manage seizures caused by tranexamic acid to minimize the risk of neurologic sequelae. The initial approach should prioritize stopping the seizures. This is typically accomplished by providing the general anesthetic, isoflurane or propofol, either through re-induction of the patient or by prolonging the duration of postoperative anesthesia (Lecker et al., 2016; Kawagishi et al., 2022). Furthermore, intravenous benzodiazepines, such as lorazepam or diazepam, can also be administered as anti-seizures (Lecker et al., 2016). Following anti-seizures administration, it is critical to conduct an extensive examination to identify the underlying factors contributing to postpartum seizures. This involves evaluating the effects of preeclampsia or eclampsia, eclampsia-related seizures, or central nervous system infections such as meningitis or encephalitis.

There were no indications of infection in this patient. The patient's medical records indicate that there were no previous histories of hypertension or preeclampsia during pregnancy (Jolly et al., 2000; Ruys et al., 2013). This is supported by the results of blood pressure and urine protein tests, which showed no abnormalities. Based on the lack of a previous occurrence of preeclampsia, eclampsia, or other identifiable causes, it was concluded that the seizures were most likely caused by tranexamic acid.

Despite the absence of renal impairment and the administration of standard doses, this case shows that even when used within the therapeutic dose, tranexamic acid can induce seizures in vulnerable individuals. For patients receiving tranexamic acid, it is critical to closely observe and monitor any neurological symptoms, particularly during the postoperative period. Alternative strategies for the management of postpartum hemorrhage may be considered in patients at higher risk of seizures (Zehtabchi et al., 2014; Montroy et al., 2018).

Conclusion

This case highlighted the potential of tranexamic acid to induce seizures, even in patients who do not have any predisposing factors that make them more vulnerable, such as renal impairment or high doses. In this case, the patient was found to have hypocalcemia, QT prolongation, and synergy when tranexamic acid was administered, potentially leading to seizures. It is critical to exercise caution when administering antifibrinolytic drugs, as they have the potential to cause side effects (Catalano et al., 2018; Maalouf et al., 2006).

It is important for doctors to be aware of the infrequent yet serious side effects associated with tranexamic acid and should closely monitor patients, particularly during the postpartum period following a cesarean section. To improve patient safety, further research is required to elucidate the mechanisms and identify the risk factors associated with tranexamic acid-induced seizures.

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