CASE REPORT

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Successful management of refractory bleeding in liver failure with tranexamic acid: Case report and literature review

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Abstract

A 50-year-old woman with advanced cirrhosis presented with spontaneous subdural hematoma. She had a worsening clinical course following craniotomy despite administration of multiple blood products. With elevation in D-dimer, persistently low fibrinogen and poor response to factor/fibrinogen replacement therapies, we had a suspicion for uncontrolled fibrinolysis. A literature review was conducted on treatment of hyperfibrinolysis in cirrhosis, finding 4 reports in which antifibrinolytics were used to control bleeding with different outcomes. The dose of tranexamic acid used in our patient was employed from previous experience in trauma patients. We transitioned from intravenous to oral administration based on expected pharmacokinetics. Our patient had a successful outcome with resolution of bleeding.

KEYWORDS

liver cirrhosis, D-dimer, fibrinolysis, spontaneous subdural hematoma, tranexamic acid

Essentials

- Uncontrolled clot breakdown with active bleeding can be seen in advanced cirrhosis.
- A literature review found little information on optimal management.
- We report a case of successful treatment with tranexamic acid for persistent subdural hematoma in this setting.

1 | INTRODUCTION

Patients with cirrhosis have rebalanced hemostasis with simultaneous decreases in pro- and anticoagulants. However, the coagulation system in these patients is very tenuous and can be tipped, resulting in hemorrhage or thrombosis.[1] Alteration in fibrinolytic pathways is reported in 30%-46% of patients with end-stage liver disease, although the exact incidence is unknown due to difficulty in diagnosis.[2] Here, we report a patient with end-stage liver disease who had a spontaneous subdural hematoma and responded to antifibrinolytic treatment with tranexamic acid (TXA). The Key Clinical Question addressed here is,

"Does TXA help to control bleeding which is refractory to factor replacement therapy in a patient with end-stage liver disease?"

2 | CASE REPORT

A 50-year-old woman awaiting liver transplantation for Child-Pugh's Class C cirrhosis due to nonalcoholic steatohepatitis presented to the emergency department with 5 days of worsening headaches, one episode of vomiting, and lethargy. A year prior, the patient had transarterial embolization of a right lobe hepatocellular carcinoma.
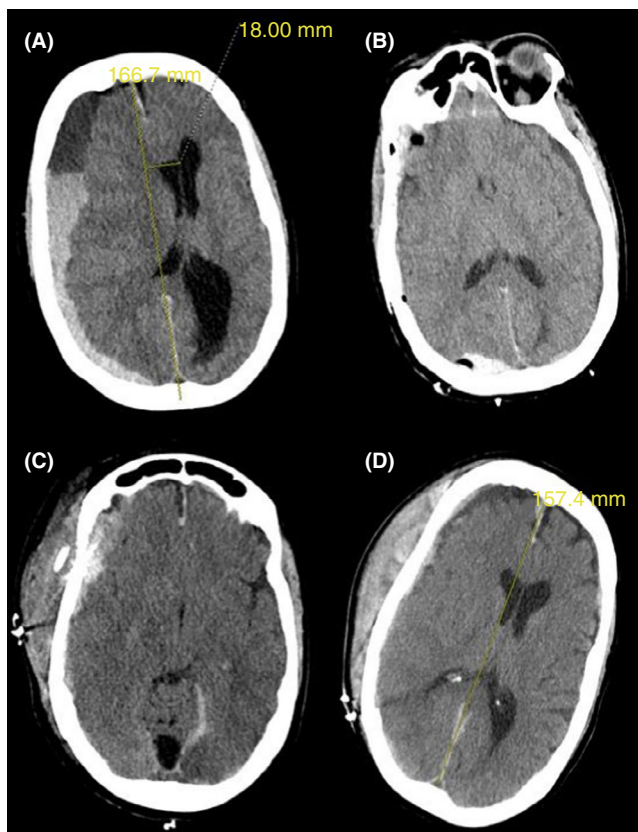
On physical examination, she was minimally alert and jaundiced with a fixed right pupil. There was no overt bleeding. Brain computed tomography (CT) showed a large 2.6-cm-diameter subdural hematoma with 2 cm of leftward midline shift (Figure 1A). Laboratory studies revealed hemoglobin 7.0 g/dL, platelet count 61 000/cmm, prothrombin time 18.1 seconds, partial thromboplastin time 42 seconds, and fibrinogen 87 mg/dL. She was given 10 mg of intravenous vitamin K, 2650 units of prothrombin complex concentrate, 3 units of red blood cells (RBCs), 2 units of apheresis platelets, and 1 pool of cryoprecipitate and was taken to the operating room for emergency decompression. Intraoperatively, she received 2 units of RBCs, 2 pools of cryoprecipitate, and 1 unit of apheresis platelets plus an additional 2 units of plasma postoperatively for ongoing bleeding. As shown in Figure 2, multiple blood products were administered during the first week of hospitalization for ongoing bleeding, totaling 16 units of RBCs, 18 units of apheresis platelets, 20 pools of cryoprecipitate, and 6 units of plasma.

She continued to be minimally responsive, with persistent oozing at the surgical site. Repeat head CT showed an increase in the size of the subdural hematoma. Plasma fibrinogen remained low, at 100 mg/dL, despite appropriate transfusion support. On hospital day 6, D-dimer was checked due to concern for hyperfibrinolysis,


FIGURE 1   Serial cranial computed tomography. (A: D1) Large subdural hematoma, leftward midline shift. (B: D2) Improvement in subdural hematoma after craniotomy. (C: D4) New scalp hematoma, worsening subdural hematoma and worsening midline shift. (D: D9) Stable scalp hematoma, decrease in subdural hematoma, decreased midline shift. D represents day of hospitalization

and was extremely elevated, at 37 890 ng/mL D-dimer units (DDUs). Kaolin-activated thromboelastography showed normal R time (reaction time: time from start of the test to initial fibrin formation), normal K time (time from initial clot formation to an amplitude of 20 mm), normal alpha angle (slope between R and K, indicating rate of clot formation and fibrin crosslinking), normal Ly-30 (amplitude at 30 minutes measuring fibrinolysis), and a decrease in maximum amplitude (representing overall stability of the clot) at 27.30 mm. The thromboelastography assay was performed following aggressive transfusion support, possibly reducing the sensitivity of the assay to detect a hemostatic or fibrinolytic abnormality. In response, on hospital day 7, TXA was started with a 2 mg/kg bolus intravenously, and continuous infusion at 200 mg/h. D-dimer decreased to 13 221 ng/mL DDU within 24 hours, and transfusion requirements decreased as depicted in Figure 2. On hospital day 8, the patient was extubated and transferred to the medical floor. TXA was decreased to 100 mg/h continuously on day 14. As imaging and D-dimer stabilized, neurologic status also improved. On hospital day 15, intravenous TXA was converted to oral dosing by starting 1300 mg of oral TXA and discontinuing the infusion 2 hours later. This was followed by administration of 1300 mg of TXA orally every 6 hours with intent to taper the dose following D-dimer. On hospital day 16, the dosing frequency was reduced to every 8 hours, but D-dimer increased from 5000 to 9900 ng/mL DDU within 12 hours, and the fibrinogen level decreased from 145 mg/dL to 120 mg/dL. As the decrease in D-dimer correlated with improvement in her neurological status and head CT findings, we were concerned that her clinical status could deteriorate with increasing D-dimer level. In response, TXA dosing frequency was empirically increased to every 6 hours, and the D-dimer remained stable. Throughout the hospital stay there was no clinical or radiologic evidence of thrombosis. On hospital day 24, the patient was transferred to a transplant center and is currently being evaluated for liver transplant.

3 | DISCUSSION

This case illustrates the potential role of antifibrinolytic medication for life-threatening bleeding in decompensated cirrhosis. Patients with liver disease have alterations in primary hemostasis, with decreases in platelet number and function; decreases in production of all procoagulant factors except factor VIII; decreases in anticoagulant proteins including antithrombin, protein C, protein S; and variable alterations in fibrinolytic proteins. However, the hemostatic milieu is rebalanced in cirrhosis.[3]

In cirrhosis, comorbidities including bacterial infection, renal disease, and portal hypertension can tip the hemostatic balance leading to bleeding.[1,3] Management of active bleeding in cirrhosis is aimed at RBC transfusions targeting hemoglobin of 7-8 g/dL, platelet transfusions for thrombocytopenia to maintain platelet counts >50 000/cmm, and transfusion of cryoprecipitate to maintain a fibrinogen level >100 mg/dL.[3] Our patient received multiple hemostatic products including RBCs, apheresis platelets, frozen
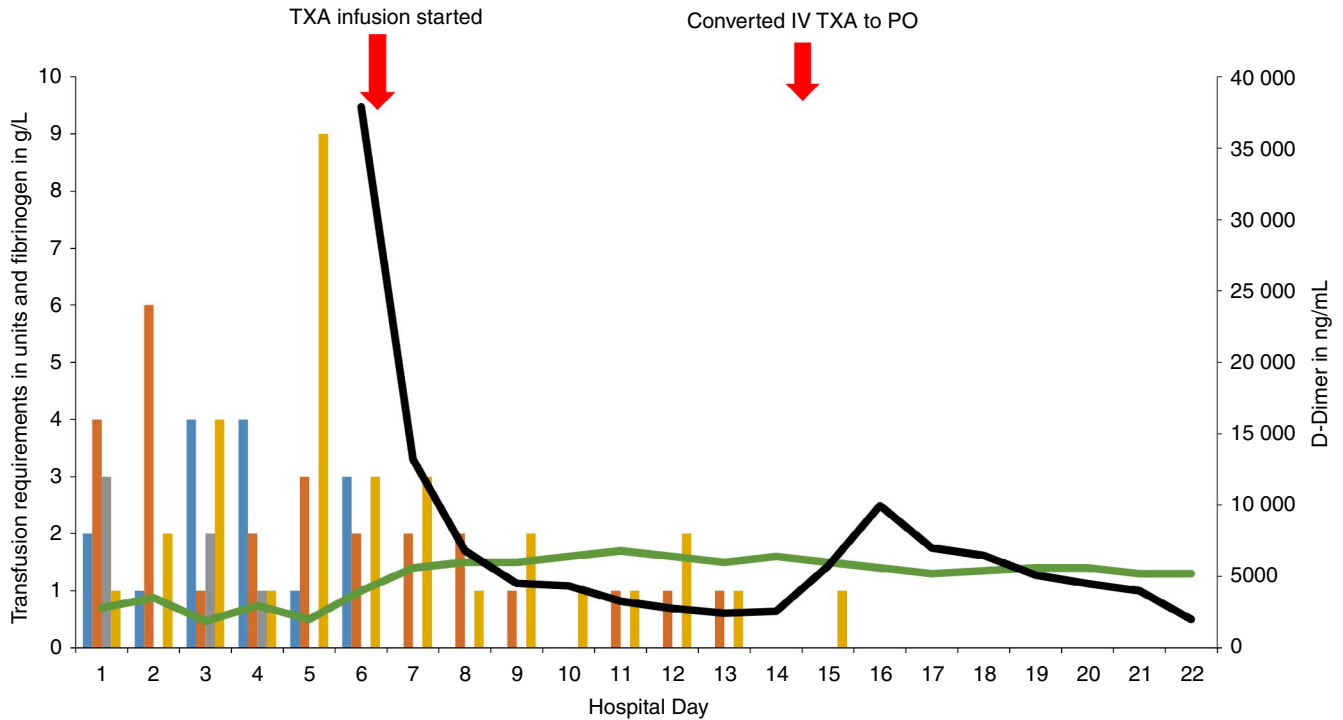
FIGURE 2 Day of hospitalization (x-axis). Total transfusion requirements, fibrinogen and D-dimer (y-axis). ■, PRBC; ■, platelets; ■, FFP; ■, Cryo; ——, fibrinogen; ——, D-dimer

plasma, and cryoprecipitate, and the clinical course worsened due to an increasing subdural hematoma and persistent hypofibrinogenemia. This, along with an extremely elevated D-dimer on hospital day 6, raised the suspicion for uncontrolled fibrinolysis, and she was treated with TXA, with rapid improvement. There could also have been a component of secondary hyperfibrinolysis from disseminated intravascular coagulation (DIC). However, the fibrinogen level, which was dropping despite cryoprecipitate infusions, stabilized on day 6 with TXA, suggesting a component of primary hyperfibrinolysis. The exact incidence of hyperfibrinolysis is unknown, partly due to a lack of appropriately sensitive laboratory tests for evaluation, although

it is reported to occur in 30%-50% of patients with end-stage liver disease.[2,4,5] Both primary and secondary hyperfibrinolysis can be seen in patients with cirrhosis. Primary hyperfibrinolysis is due to impaired synthesis of α2 antiplasmin and thrombin-activatable fibrinolysis inhibitor leading to accelerated fibrinolysis (Figure 3). Secondary hyperfibrinolysis in liver disease occurs in the setting of DIC.[5] Several assays have been developed to detect hyperfibrinolysis, including the euglobulin clot lysis time, dilute whole blood clot lysis time, turbidimetric plasma clot lysis assay, global fibrinolytic capacity in the whole blood, and thromboelastography. However, none of these assays are sensitive enough to detect hyperfibrinolysis in
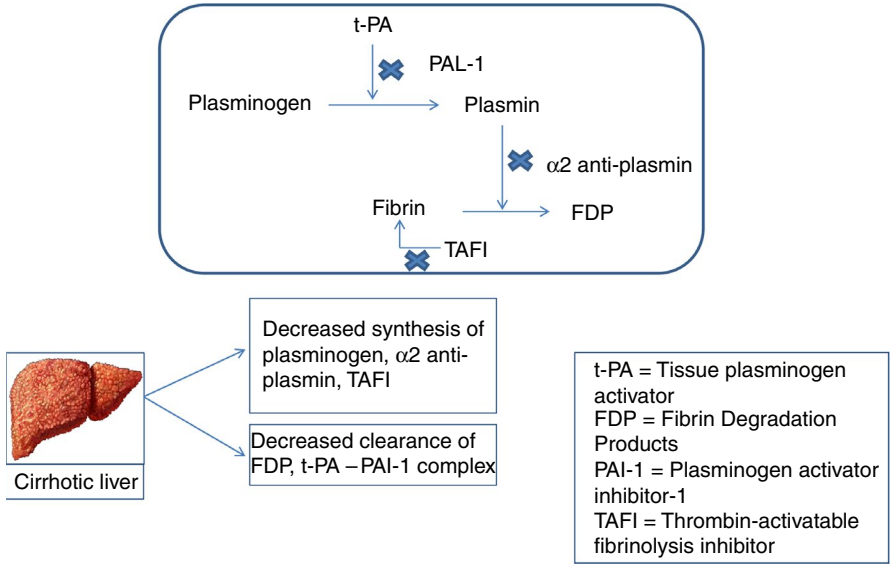
FIGURE 3 Pathophysiology of hyperfibrinolysis in cirrhosis

TABLE 1 Summary of case reports with antifibrinolytics in cirrhosis-related bleeding

Authors	Number of patients	Age/sex	Presentation/indication	Treatment type/dosing	Outcome
Gunawan et al[15]	52	Mean age 49.6 y (32-67) Males, 73%	Study included 37 bleeding patients and 15 patients with no bleeding but shortened euglobulin clot lysis time	EACA-1 g q6h	37 bleeding patients—34 had resolution of bleeding, 2 patients with no improvement, 1 patient died 15 patients without bleeding—14 did well with no bleeding episodes, 1 had melena and died from liver failure complications
Nair et al[16]	1	65/male	Cirrhosis with spontaneous intramuscular hematoma	EACA 150 mg/kg loading dose followed by 1 g q4h × 2	Resolution of bleeding
Laskiewicz et al[17]	1	72/male	Advanced cirrhosis with bleeding	TXA 1000 mg intravenous bolus followed by 1000 mg IV over 8 h on days 16, 18, and 23	Expired on day 23 from pulseless electrical activity
Louro et al[18]	1	69/male	Bleeding from blunt abdominal trauma	Factor VIIa 1 mg and TXA 1 g i.v. bolus	Expired from multiorgan failure

Note.. Abbreviations: EACA: ε-aminocaproic acid; TXA; tranexamic acid.

cirrhosis due to the complex interactions between pro- and antifibrinolytic pathways.[4,6–8] Hugenholtz et al[9] similarly found normal thromboelastography lysis times for cirrhotic patients, although median Ly-30 time decreased with advanced cirrhosis.

It was difficult to prove hyperfibrinolysis in our patient with conventional laboratory studies, but there was a high index of suspicion due to persistent hypofibrinogenemia, extremely elevated D-dimer levels, and ultimately the response to TXA treatment. Unfortunately, frozen plasma was not available to perform any of the assays developed to detect hyperfibrinolysis as described above. Review of the literature on treatment of hyperfibrinolysis in liver disease was conducted using PubMed from 1980 to 2017. There were no randomized controlled trials demonstrating the role of antifibrinolytics for bleeding in patients with end-stage liver disease. Antifibrinolytics have been studied primarily in the control of bleeding in trauma patients.[7,10–12] They have also been studied to decrease transfusion requirements during liver transplantation.[13,14] Gunawan et al[15] reported the benefit of ε-aminocaproic acid (EACA) to treat hyperfibrinolysis in a case series of 52 patients with cirrhosis. Of the 52 patients, 37 patients received EACA due to bleeding episodes, with subcutaneous/soft tissue bleeding being the most common type. Fifteen of 52 patients received EACA due to shortened euglobulin lysis time or prior to an invasive procedure but had no signs of bleeding. Nair et al[16] published a case report in which EACA was successfully employed to treat hyperfibrinolysis with spontaneous intramuscular hematoma in cirrhosis. TXA was used by Laskiewicz et al[17] to control refractory bleeding that manifested as persistent oozing at the catheter sites in a patient with cirrhosis, but the patient died of sepsis. Louro et al[18] used TXA and factor VIIa to correct coagulopathy and hyperfibrinolysis in a patient with cirrhosis who sustained a blunt abdominal injury from a motor vehicle collision, but the patient died from multiorgan failure. Table 1 shows a summary of reports in which antifibrinolytics were used in cirrhosis-related bleeding.

Tranexamic acid is a synthetic lysine analogue and mimics lysine residues on fibrin, to which plasminogen normally binds.[19,20] It prevents fibrinolysis by binding to plasminogen, preventing its conversion to plasmin. It can directly inhibit plasmin activity at higher doses.[10] TXA was also shown to attenuate the inflammatory response in trauma patients with survival benefit.[12] There is no general consensus on the dosing of TXA for hyperfibrinolysis in cirrhosis. It can be given as an intravenous (i.v.) bolus (20-25 mg/kg) followed by continuous infusion at 1-2 mg/kg/h or 1 g over 10 minutes followed by 1 g over 8 hours.[10] We chose to give an i.v. bolus, then a continuous infusion at 2 mg/kg/h. The D-dimer markedly decreased within a day of infusion, there were no thrombosis complications, and the clinical course improved (Figure 2). Risk of thrombosis in patients with DIC and hyperfibrinolysis receiving TXA should be considered, as enhanced coagulation activity from DIC compounded by shutdown of the fibrinolytic pathway from TXA can increase the risk for thrombus formation.[21] However, there are very limited data on TXA and increased risk for thrombosis in patients with hematologic disorders.[20] Thus, it is reasonable to consider administration of TXA in a patient with life-threatening bleeding.[22]

4 | CONCLUSION

This case report is the first that we are aware of in which TXA was successfully employed to control life-threatening bleeding in a patient with end-stage cirrhosis. Our patient received substantial transfusion support aiming to correct primary hemostatic and coagulation abnormalities, but her bleeding persisted. This raised a suspicion for hyperfibrinolysis, although it was difficult to prove with conventional laboratory studies. It is possible that bleeding was due to primary hyperfibrinolysis or secondary hyperfibrinolysis from DIC. Recognition of uncontrolled fibrinolysis may prevent morbidity

and mortality in similar cases. Earlier identification in this case might have shortened the hospitalization.

RELATIONSHIP DISCLOSURE

The authors have no relationships to disclose.

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