Anesthetic management of massive gastrointestinal bleeding during endoscopic sclerotherapy in a child with end stage liver disease due to Langerhans cell histiocytosis

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**Goals/Objectives:**

1. Describe the clinical manifestations of Langerhans cell histiocytosis and the anesthetic considerations in caring for a child with end stage liver disease.

2. Discuss the role of the pediatric anesthesiologist in initiating a massive transfusion protocol and in treating ongoing hemorrhage and coagulopathy in the pediatric patient.

3. Discuss all treatment options available to the pediatric anesthesiologist to control bleeding, including the involvement of other services such as interventional radiology or general surgery.

4. Review the ethical considerations of when to stop a massive transfusion protocol including a patient’s expiration due to exsanguination.

**Case Description:**

A 2-year-old, 12 kg male with end stage liver disease due to Langerhans cell histiocytosis presented to ICU with massive hematemesis. He had been diagnosed with Langerhans cell histiocytosis after presenting with liver failure of unknown cause at age nine months. He failed his initial chemotherapy regimen and his disease progressed to involve lymph nodes, skin, and bone, and worsening liver failure with development of esophageal and gastric varices. A recent PET CT showed that he was finally in remission, though his end stage liver sequelae continued to worsen. He was evaluated for possible liver transplant, but was deemed not to be a candidate because he had not been in remission for at least six months. It was also thought that TIPS or surgical portosystemic shunt carried an unreasonably high risk of morbidity/mortality. Transhepatic coiling/embolization of varices by interventional radiology had been discussed, and the patient had undergone a CT with venous mapping for this procedure the day before. In the meantime, his intermittently bleeding varices were being controlled by endoscopy/sclerotherapy as needed while he awaited further intervention and possible candidacy for liver transplant.

QUESTIONS: What is Langerhans cell histiocytosis? What implications does liver involvement have in terms of prognosis? What are the anesthetic implications of end stage liver disease of any cause? What treatments are available for patients with Langerhans cell histiocytosis and liver failure? Are they candidates for liver transplant? What are other anesthetic concerns for a patient with this disease?

The patient was admitted to the ICU with ongoing hematemesis around midnight. There, he was intubated by the anesthesiology fellow for airway protection, transfused 15mL/kg pRBCs and started on an epinephrine infusion for hemodynamic support by the ICU team. He had a 22g PIV for access. The hepatologist and intensivist agreed that the child should be transported to the OR for emergency sclerotherapy of bleeding varices and called the anesthesiologist on call.
QUESTIONS: How would you assess whether the patient is stable enough to go to the OR? What additional clinical information would you require prior to making your decision? What additional resuscitation would you require prior to transport? What would you tell the family?

What other options are available to control bleeding besides sclerotherapy? Are there any other teams you want involved? Would you involve them from the beginning, or what you wait to see how the case is going?

What is your monitoring plan? What is your induction plan? What is your maintenance plan?

Upon arrival to the OR, the child was hemorrhaging profusely from the nose and mouth. He was edematous and hypotensive, which complicated efforts to secure additional venous and arterial access in the setting of ongoing hemorrhage. Following successful placement of a femoral venous line and an arterial line, the first arterial blood gas showed a pH of 7.19, base deficit of -6, and hemoglobin of 3.4 gm/dL.

QUESTIONS: When and how do you decide to initiate a massive transfusion protocol?

What are the underlying conditions in liver disease that favor hemorrhage? How does the coagulopathy of liver failure differ from other coagulopathies? How is it similar? Are standard coagulation studies (measurement of prothrombin time and activated partial-thromboplastin time) reliable in patients with coagulopathy due to liver failure? How are platelets affected in liver failure? How is thrombin generation affected in liver failure? Is liver failure a hyperfibrinolytic or hypofibrinolytic state? Are patients with liver failure protected from thrombosis, or are they at an increased risk?

How would you monitor the coagulation status in this patient? What is thromboelastography (TEG) and how does it differ from standard coagulation studies? Would TEG would be helpful in this case? What other procoagulant agents are available to aid in obtaining hemostasis?

The patient continued to hemorrhage during endoscopy and the gastroenterology team was unable to isolate and sclerose the source of bleeding, though it was thought to be at the gastroesophageal junction. TEG was used to aid in coagulation monitoring. After initial resuscitation, TEG showed thrombocytopenia and low fibrinogen. A total of 8u pRBCs, 4U platelets, 4U FFP, and 2U cryoprecipitate were administered, with total blood product volume of 3956 mls. Two doses of Novoseven were administered. After 3.5 hours, the source of bleeding was still not controlled. Follow-up TEG was within normal limits though the child continued to bleed uncontrollably. The decision was made by hepatology team to transport child back to the ICU for comfort care. He expired less than 24 hours following the procedure.

QUESTIONS: Is it solely the responsibility of the surgical service (or in this case the hepatology service) to determine whether a procedure or intervention is futile? What are other options used to control acute variceal bleeding? Can any of these be used in small pediatric patients? Would they have been appropriate to use in this child at this time? Is there a role for the pediatric anesthesiologist to suggest the need for further intervention? Is there a role for the pediatric anesthesiologist to arrange for further intervention even without the agreement of the hepatologist? How do you feel about the outcome of this case?
Discussion:

Langerhans cell histiocytosis (LCH) is a proliferative disorder characterized by histiocyte infiltration and accumulation in several types of tissues. Langerhans cells are generally localized to epithelial surfaces, and their immunologic function is to transport foreign antigens to T cells within the lymphatic system. The cause of LCH is unclear, though it may represent an autoimmune phenomenon. A definitive diagnosis includes identification of clinical features in addition to histopathologic and immunohistochemical results. LCH is defined with regard to its involvement of a single system, multiple systems, and single organ or multiple organs. In pediatric patients, the most common presentation is multiorgan disease (50-70%). Because of the diverse spectrum of possible clinical features, it is imperative to consider a particular patient’s disease manifestations when caring for them perioperatively. Prognosis is dependent on the number of organs involved, the presence of organ dysfunction, and the patient’s age. Involvement of the spleen, liver, lung, or hematopoietic system suggests a poor prognosis (Drutz, 2011). The best prognostic indicator is a patient’s response to the induction phase of chemotherapy. For patients that do not show an early response, survival rates drop precipitously low (Satter et al., 2008).

Long term sequelae of LCH can occur even with adequate treatment, and include sclerosing cholangitis and liver failure. Liver dysfunction impairs several important steps required for normal hemostasis and, when advanced, results in a generalized hypocoagulable state. Despite the known risk of bleeding associated with end-stage liver disease, the concept that life-threatening hemorrhage occurs secondary to an overall dysfunction of the coagulation system has recently been challenged (Tripodi and Mannucci, 2011). Decreases in the level of procoagulant proteins are accompanied by similar decreases in anticoagulant proteins so that the coagulation system remains balanced by these two opposing forces. In addition, the basic laboratory tests used to assess the risk of bleeding (PT and aPTT) have been shown to correlate poorly with actual hemorrhagic episodes after liver biopsy and other invasive procedures (Tripodi and Mannucci, 2011). The old paradigm that the bleeding observed with liver disease is strictly a result of hypocoagulability is being replaced by a new paradigm in which the bleeding diathesis associated with liver dysfunction is triggered by underlying conditions that favor hemorrhage, i.e. the presence and severity of portal hypertension and renal failure, endothelial dysfunction, and bacterial infections (Tripodi and Mannucci, 2011).

Despite this new paradigm, there are several major alterations in the hemostatic pathways of children with liver disease that are worthy of review. Thrombocytopenia is present in up to 70% of patients with severe liver disease even though platelet production may be normal or increased. The causes of thrombocytopenia are multifactorial and include platelet sequestration from portal hypertension and splenomegaly, shortened platelet survival, decreased thrombopoietin synthesis, folic acid deficiency, and immune complex-associated platelet destruction. Quantitative platelet dysfunction is also observed, especially impaired aggregation. Most consensus guidelines recommend maintaining platelet counts at 50-100 x 10^9 L^-1.

All of the coagulation factors, except for FVIII, are synthesized in the liver and, with declining liver function, become markedly diminished. A poor nutritional state and a reduction in bile salts decrease the absorption of fat soluble vitamins (A, D, E and K) and contribute to a functional deficiency in factors II, VII, IX and X. Diseased liver cells also fail to enzymatically remove sialic acid from fibrinogen resulting
in dysfibrinogenemia. Parallel reductions in most physiologic anticoagulants, including AT, PC and PS, are also observed. In contrast, levels of FVIII are markedly increased and, as a result, patients with cirrhosis are capable of generating normal to elevated amounts of thrombin (Tripodi and Mannucci, 2011).

Coagulation screening tests, initially the PT and INR and later the aPTT and thrombin time (TT), are prolonged. The PT, INR and FV and FVII levels are often used as markers of hepatocellular function and prognosis for advanced liver disease. The INR is included in most criteria used for evaluating and scoring fulminant liver failure and/or end-stage liver disease. However, recent studies have raised serious concerns regarding the use of the PT and INR to predict bleeding risk in advanced liver disease (Tripodi and Mannucci, 2011). Thus the administration of FFP and other coagulation factors should not be administered prophylactically and based on arbitrary cutoff values, but rather based on the clinical scenario.

Fibrinolysis is also impaired in severe hepatic dysfunction. Especially during the latter stages of disease when coagulation factors are rapidly consumed, accelerated fibrinolysis with elevated levels of fibrin split products and D-dimers may be observed. A recent study in children with chronic liver disease from various causes found that D-dimer levels in the children with cirrhosis of Child class A and B were significantly higher than in the noncirrhotic and control groups (El-Sayed et al., 2013). The role of antifibrinolytic therapy in pediatric patients with significant liver dysfunction presenting for surgery is unclear, though a recent Cochrane Database Review comparing the potential benefits of different methods of decreasing blood loss and blood transfusion requirements during liver transplantation found that aprotinin, tranexamic acid, rFVIIa, low central venous pressure, and thromboelastography may lower blood loss and transfusion requirements (Gurusamy et al., 2011).

The perioperative management of children with significant liver disease should include a complete evaluation of their coagulation profile and a targeted approach to correcting deficiencies. When indicated, vitamin K is a useful in normalizing a prolonged PT. FFP may also be used to correct clotting factor deficiencies but the large volume required to adequately replete clotting factors is often poorly tolerated by these patients. In such a situation, prothrombin complex concentrates may be a useful alternative. Hypofibrinogenemia should be corrected with cryoprecipitate. Experience with rFVIIa in children with end stage liver disease is limited. However, several studies suggest that it may be beneficial as rescue therapy to control severe hemorrhage.

The field of anesthesiology has changed significantly over the years. We have expanded from just providing unconsciousness during surgical procedures to being true perioperative physicians. Because of our expertise in physiology and pharmacology, we play a crucial role in managing complex physiology and maintaining homeostasis both inside and outside the operating room. It is often the anesthesiologist that is most familiar with a perioperative patient’s coagulation status, and must direct treatment to achieve and maintain hemostasis, including determining which coagulation studies are appropriate, which blood products or procoagulant agents to administer, and whether to activate or stop a massive transfusion protocol. It follows then that the anesthesiologist should have an inherent role in deciding how this information can be used to guide surgical or interventional treatment. To reaffirm our roles as professional perioperative physicians we must communicate effectively with our colleagues in other specialties to show them that we are sincere and committed to our expanded roles.
References:


