

Recombinant Factor VIIa and Tranexamic Acid in Subgaleal Hemorrhage

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Submitted: 20 Aug 2016; Accepted: 17 Sep 2016; Published: 22 Sep 2016

Introduction

Subgaleal hemorrhage (SGH) is a severe condition associated with a 5-14% risk of neonatal death. SGH has been described as a complication of birth by vacuum extraction; however it can occur with any mode of delivery. The spectrum of clinical severity varies from mildly asymptomatic to severe, with hemorrhagic shock, coagulopathy and end organ injury. Early recognition of symptoms, prompt restoration of circulatory volume and control of bleeding could improve outcomes [1].

Recombinant activated factor VII (rFVIIa) is approved by the United States Food and Drug Administration (FDA) for patients with hemophilia A and B who have inhibitors to factor VIII or IX. It is used off label for the treatment of refractory hemorrhage in infants and children. Tranexamic acid, an anti-fibrinolytic agent also used in pediatric surgery to prevent bleeding. Limited evidence exists for use of both rFVIIa and Tranexamic acid to treat SGH.

Case Report

A term male infant with birth weight of 3250 gm was born to a primigravida diagnosed clinically with non-vascular Ehler-Danlos syndrome following an uneventful pregnancy. There was no family history of bleeding. Vertex delivery followed 2 applications of the vacuum cap for failure to progress and fetal tachycardia. The infant was pale and hypotonic at birth requiring positive pressure ventilation for less than 1 minute. The APGAR scores given were 4 at 1 minute and 7 at 5 minutes with a cord blood pH of 7.30.

He was noted to be pale, lethargic, tachycardic (180 bpm) and hypotensive on admission to NICU shortly after birth. A soft boggy swelling was noted over the occiput. Tachycardia and perfusion improved following a 10 ml/kg bolus of saline. Hematocrit on admission was 0.32. He received a further 10 ml/kg bolus of normal saline for sluggish perfusion and metabolic acidosis pH 7.22, base deficit of -13 and lactate of 8.

At 3 hours of age his head circumference had increased by 2 cm from birth however heart rate and blood pressure were within normal limits. He required intubation at 4 hours of age for bradycardia and

apnea requiring bag and mask ventilation. He required extensive cardiopulmonary resuscitation including chest compressions, fluid boluses and intravenous adrenaline for cardiac arrest lasting 16 minutes. His blood gas during circulatory arrest showed severe metabolic acidosis with pH <6.8 an incalculable base deficit, lactate of 18 and hematocrit of 0.1. Cardiac output was sustained following restoration of circulatory volume with 50 ml/kg packed red blood cells (PRBC) given in 50 ml syringe aliquots pushed via umbilical venous line, fresh frozen plasma (FFP) of 40 ml/kg given in 50 ml syringe aliquots, 2 units of cryoprecipitate, 1 unit of platelets and 20 ml/kg of normal saline given as boluses. He also required multiple inotropes and hydrocortisone to treat intractable hypotension after volume replacement.

He received a further 50 ml/kg of PRBC, 45 ml/kg of FFP, 2 units of cryoprecipitate and 3 units of platelets to treat anemia, coagulopathy and thrombocytopenia following resuscitation. A Cranial ultrasound confirmed clinical suspicion of massive SGH. His head circumference had increased by a 7 cm from birth on day 1 of life. He developed disseminated intravascular coagulopathy (DIC) with deranged coagulation profile, thrombocytopenia and anemia persisting despite multiple transfusions of FFP, platelets, cryoprecipitate and PRBC. In consultation with Pediatric Hematology, 3 doses of intravenously rFVIIa at 60 microgram/kg/dose were given over 9 hours for severe SGH with evidence of ongoing bleeding and DIC. He was also commenced on 10mg/kg/dose of intravenous Tranexamic acid three times a day. Bleeding significantly decreased following combined administration of rFVIIa and tranexamic acid. He required only 1 PRBC, FFP and cryoprecipitate transfusion after starting tranexamic acid and rFVIIa. His laboratory coagulation parameters stabilized after the first 2 doses of rFVIIa. INR improved from 4.2 to 1.4, PTT stabilized from >150 to 28 and fibrinogen improved from 0.7 to 2.1. Tranexamic acid dose was reduced to 10 mg/kg/day on Day 3 in view of acute tubular necrosis (ATN). Tranexamic acid was discontinued after 10 days with no further evidence of bleeding.

The infant had hemorrhagic hypovolemic shock induced multi-organ dysfunction, encephalopathy with clinical and electrographic seizures, oliguria and hepatic dysfunction. Therapeutic hypothermia was

considered but not instituted due to severity of DIC with bleeding. An MRI brain on day 6 after stabilization showed subgaleal, subdural and epidural hemorrhages with T1 and T2 weighted changes within the cortex of both cerebral hemispheres suggestive of partial prolonged ischemia with sparing of the basal ganglia. Ultrasound and MRI abdomen showed a splenic hematoma, hemoperitoneum and bilateral adrenal hemorrhages. Inotropes were discontinued after 48 hours and he was extubated after 9 days of ventilation.

Acute renal injury (ATN) and elevated liver enzymes resolved with conservative management. He however developed hypertension presumed to be of renal origin requiring treatment with hydralazine. His neurologic status and physical examination at discharge was normal except for mild truncal hypotonia. He was discharged from hospital at one month of age on phenobarbital and hydralazine. He was off all medication by 4 months of age and at 18 months he had a normal neurological examination except for mild gross motor delay. He subsequently presented with spontaneous subluxation of shoulder joint and clinical features of hypermobility joint disorder and is being investigated for Ehler Danlos syndrome.

Discussion

Early recognition and aggressive management of hypovolemic hemorrhagic shock in symptomatic SGH can reduce mortality and severe morbidity. Hypovolemic shock requires prompt use of PRBC, FFP, cryoprecipitate and platelets to re-establish circulatory volume to prevent hypo-perfusion related end organ injury and to treat associated coagulopathy. Infants with refractory hemorrhage despite FFP, cryoprecipitate and platelets may benefit from rFVIIa and Tranexamic acid as described in this case report.

rFVIIa acts by binding to tissue factor or by directly activating factor X on the surface of activated platelets resulting in thrombin burst which leads to the formation of a stable hemostatic plug which controls bleeding. Dang et al. evaluated 18 neonates who received at least one dose of rFVIIa in a retrospective cohort study for the treatment of pulmonary hemorrhage, gastrointestinal hemorrhage, post-surgical bleeding, intracranial hemorrhage, superficial skin hemorrhage and DIC [1]. Hemostasis was achieved in 72% of infants within 72 hours of rFVIIa administration. There is limited evidence for the use of rFVIIa in the management of SGH. Strauss et al. in a case report used 4 doses of rFVIIa, 100 microgram/kg/dose every 2 hours in an infant with refractory SGH. Bleeding eventually stopped however the infant died 2 weeks later from multi organ failure [2]. Hunseler et al. reported the use of 120 microgram/kg/dose of rFVIIa in an infant with subgaleal hemorrhage and demonstrated cessation of bleeding and normalization of coagulation parameters [3]. rFVIIa is used at the dose of 90 microgram/kg/dose for the treatment of hemophilia A or B with inhibitors. Studies have shown that doses ranging from 40-300microgram/kg have been used off label, depending on the indications and severity of bleeding in neonates. We used 3 doses of 60 microgram/kg/dose of rFVIIa every 3 hours and found this to be effective in the case described. Adverse events reported following the use of rFVIIa in adults include cerebrovascular accidents, arterial thrombosis, venous thrombosis and pulmonary embolism. Puetz et al. found no difference in the incidence of thrombotic events in neonates who received rFVIIa (132 infants) and neonates who received FFP for coagulopathy [4]. No thrombotic event was noted in our case report. Dang et al. found that clinical hemostasis was not achieved in 28%

of infants treated with rFVIIa especially in severe DIC [5]. In those instances addition of an anti-fibrinolytic agent may be beneficial. Tranexamic acid acts by competitive inhibition of plasminogen activation. It has been used mainly to reduce peri and post-operative blood loss in infants undergoing cardiac surgery, trauma, and craniofacial surgery and in children with hemophilia. There is not much evidence for the use of tranexamic acid in neonatal subgaleal hemorrhage. Strauss et al. reported the first use of tranexamic acid along with rFVIIa for a neonatal subgaleal hemorrhage and found this to be effective in control of bleeding [3]. We further add to this evidence that rFVIIa and tranexamic acid are useful adjuncts in the management of severe refractory SGH.

Conclusion

Subgaleal hemorrhage can be massive and associated with severe DIC. Our case highlights the importance of close monitoring, early recognition and aggressive volume replacement aimed at restoring circulatory volume promptly to minimize end organ injury. The authors recommend involvement of a pediatric hematologist to guide management of associated coagulopathy and consideration of rFVIIa at moderate doses with an anti-fibrinolytic as second line therapy for cases refractory to standard blood product support.

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