Pediatric Anesthesia and Critical Care Journal 2021;9(1):36-42
doi:10.14587/paccj.2021.6

PACCJ

Perioperative care of an adolescent with hemophilia B undergoing posterior spinal fusion

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Keypoints

1. Hemophilia B or Christmas disease is a coagulation disorder resulting from the congenital or acquired deficiency of clotting factor IX. It is inherited as a X-linked disorder and is the second most common type of hemophilia.
2. The development of novel plasma derived and recombinant factor IX preparations have allowed for the achievement of plasma concentrations high enough to prevent or stop bleeding as well as decreasing or eliminating the transmission of viral diseases.
3. The primary therapeutic endeavor in the perioperative management of patients with hemophilia B patients remains the administration of and precise control of factor IX levels.
4. During major surgical procedures, a factor IX level ≥ 80% of normal is generally recommended. During perioperative care, a continuous infusion may be chosen over bolus dosing to ensure the maintenance of therapeutic factor IX levels.

Abstract

Hemophilia B is a coagulation disorder related to the deficiency of clotting factor IX. Depending on the severity of the deficiency, patients may experience significant hemorrhage spontaneously or following minor trauma. Additionally, given the associated coagulation defect, any surgical procedure or traumatic event carries the risks of severe hemorrhage, an increased incidence of perioperative complications, and even death. We present a 13-year-old adolescent who was diagnosed with hemophilia B during investigation for a prolonged partial thromboplastin time during a routine preoperative laboratory evaluation. The perioperative management of a newly diagnosed hemophilia B patient is discussed including the perioperative administration of blood, blood products, and coagulation adjuncts.

Keywords

hemophilia B, posterior spinal fusion, factor IX

Introduction

Hemophilia B is a coagulation disorder resulting from the congenital or acquired deficiency of clotting factor IX. The disorder is also known as Christmas disease, as it was named for a 5 year old boy who was the first patient described in a case series of 7 patients in 1952.[1] Hemophilia B is inherited as a X-linked disorder, has an incidence of approximately 1 in 30,000 males, and is the second most common type of hemophilia.[2,3] The symptoms and severity of hemophilia B vary based on the factor IX levels. Individuals with mild hemophilia have factor IX levels between 5-40% of normal; those with moderate hemophilia have factor levels 1-5% of normal; and individuals with severe hemophilia have factor levels less than 1% of

normal. Bleeding episodes may be severe and spontaneous in patients with severe hemophilia while mildly affected patients may have limited clinical consequences of the disorder with bruising and bleeding only after surgery, dental procedures, injury, or trauma. Patients with mild hemophilia B may go undiagnosed until a surgical procedure is needed, or an injury occurs. We present a 13-year-old adolescent who was diagnosed with hemophilia B during investigation for a prolonged active partial thromboplastin time (APTT) during routine perioperative lab work. The perioperative management of a newly diagnosed hemophilia B patient is discussed including the perioperative administration of blood, blood products, and coagulation adjuncts.

Case report

Review of this case and presentation in this format was in accordance with guidelines of the Institutional Review Board at Nationwide Children's Hospital (Columbus, Ohio). A 13-year-old, 55.5 kg male with adolescent idiopathic scoliosis presented for preoperative work-up 1 month prior to a scheduled posterior spinal fusion to treat idiopathic scoliosis. His past medical history, other than his presenting adolescent idiopathic scoliosis, included acne vulgaris and seborrheic dermatitis of the scalp. As he was adopted, there was limited information regarding his birth history. His past surgical history included a tooth extraction with some concern that there had been prolonged bleeding. Review of systems was unremarkable. Physical exam demonstrated a healthy appearing male adolescent with normal vital signs and physical examination. During routine preoperative coagulation function evaluation, the prothrombin time (PT), APTT, and international normalized ratio (INR) were 13 seconds (normal: 12.4-14.7 seconds), 44 seconds (normal: 24-36 seconds), and 1.00 (normal: ≤1.3), respectively. Subsequent work-up revealed a quantitative factor IX level of 10% (normal: 64-216%). Quantitative factor VIII, XI, and XII levels were normal. The pediatric hematology consultants concluded that his results were consistent with mild factor IX deficiency, Hemophilia B. Recommendations included correction of factor IX levels using a continuous infusion of a factor IX product with close monitoring of factor IX levels during the perioperative period. On the day of the procedure, treatment was initiated with a recombinant factor IX product (BeneFIX, Pfizer, New York, NY) with a bolus of 6,660 IU (120 IU/kg) followed by a continuous infusion of 440 IU/hour (8 IU/kg/hr) administered via a peripherally inserted central catheter (PICC). Prior to the start of surgery, the factor IX level after the initial bolus and start of the infusion was 132%. The patient was held *nil per os* for 6 hours and transported to the operating room where routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced with propofol (200 mg), fentanyl (100 µg), and lidocaine (80 mg). Tracheal intubation was facilitated by the administration of rocuronium (20 mg). Following the induction of anesthesia and endotracheal intubation, two peripheral intravenous catheters and a radial arterial cannula were placed. Based on our usual practice to facilitate somatosensory and motor evoked potential monitoring, anesthesia was maintained with desflurane in air/oxygen, lidocaine (1 mg/kg/hour), methadone, and a sufentanil infusion.[4] The patient was positioned prone on the operating room table. Tranexamic acid was administered according to institutional protocol as a bolus dose of 50 mg/kg followed by an infusion at 5 mg/kg/hour.[5,6] To ensure adequate coagulation function, rotational thromboelastometry (Rotem®) was monitored intraoperatively. Additional intraoperative medications included dexamethasone (4 mg), cefazolin (2 grams) for surgical site infection prophylaxis, and ondansetron (4 mg). Surgical time was 4 hours and 19 minutes. Estimated blood loss was 600 mL and intraoperative fluids included 1000 mL of Normosol®-R and 500 mL of 5% albumin. No other blood or blood products were transfused. After completion of the surgical procedure, the patient was turned supine onto the hospital bed and following return of protective airway reflexes, demonstration of adequate spontaneous ventilation, and purposeful movements, the patient's trachea was extubated. He was

then transported to the post-anesthesia care unit with supplemental oxygen until he was fully awake, alert, and oriented. Postoperative analgesia was provided by hydromorphone delivered via a patient controlled device (PCA) and intravenous acetaminophen. This was transitioned to oral oxycodone as needed when he was tolerating a regular diet. A quantitative factor IX level drawn immediately during the postoperative period was 138%. He was discharged to the inpatient ward for additional monitoring and continuation of the factor IX infusion via the PICC. On postoperative day (POD) 1, the quantitative factor IX levels was 77%. The remainder of his postoperative course was unremarkable, and he was discharged home the evening of POD 2. Per hematology's recommendation, the recombinant factor IX infusion was continued for a total of 4 days postoperatively. The remainder of his postoperative course was unremarkable. Hematologic and orthopedic postoperative follow-up appointments were unremarkable.

Discussion

Hemophilia B is a rare hematologic disorder that presents various challenges in the perioperative setting. In severe cases of hemophilia B, frequent, spontaneous bleeding episodes are the most common symptom. These frequently include bleeding into the muscles and joints following minor trauma (hemarthrosis). These episodes are acutely associated with pain and swelling while repeated episodes lead to long-term damage including inflammation of the membrane lining the joints (synovitis), joint disease (arthropathy) with restricted movement of the affected joint. Spontaneous joint bleeding is the most common symptom of severe hemophilia B.

Complications stemming from this disease vary greatly based on severity, ranging from no spontaneous bleeding to severe spontaneous bleeding several times per month in untreated individuals.[2,3,7] In severe cases, patients will often experience their first spontaneous bleed during their first 2 years, with the first bleed sometimes occurring after circumcision. In contrast, mildly or moderately affected males may not be diagnosed until later in life. The initial presentation varies significantly with some patients, as was the case with our patient, being diagnosed based on a prolonged PTT obtained during routine preoperative evaluation. While undiagnosed individuals with mild to moderate disease can remain mostly asymptomatic, even a mild coagulation defect poses a substantial risk in the setting of major surgical procedures.

There has been a shift in the paradigm regarding the need for preoperative laboratory evaluation including coagulation screening. In our practice, prior to major surgical procedures such as spine surgery, craniotomy or surgery for congenital heart disease, routine evaluation of coagulation function including a platelet count, PT, PTT, and INR are still obtained. However, current recommendations for preoperative screening have tended to not recommend such a practice.[8-10] Coagulation studies are reserved for patients with a positive family history of bleeding disorders, a prior history of clinical bleeding, medical conditions that predispose to bleeding, and for those taking anticoagulant medications. However, this practice would have missed the coagulation defect in our patient which may have resulted in intraoperative or postoperative bleeding consequences.

In patients with hemophilia and other coagulation defects who require surgical interventions, specific preoperative care may be indicated. These include consultation with hematology specialists, inhibitor screening/titers, targeted factor replacement, use of adjunctive agents such as tranexamic acid, intraoperative monitoring of factor levels and coagulation function, as well as the availability of blood and blood products.[11-14] These issues are of paramount importance during major surgical procedures such as spine surgery, as these procedures may be associated with significant blood loss and thus may require transfusion therapy.[15,16]

The primary therapeutic endeavor in the perioperative management of patients with hemophilia B patients remains the administration of and precise control of factor IX levels. Under the World Federation of Hemophilia guidelines, the current standard of care for patients with

hemophilia B undergoing any invasive procedure includes recombinant factor IX replacement and coagulation adjuncts such as tranexamic acid (TXA).[17] The replacement of both factor IX and its adjuncts are vital, as they serve critical roles in the coagulation cascade.[18] This cascade, composed of internal, external, and common pathways, is responsible for forming an insoluble fibrin clot capable which prevents major blood loss in the setting of a traumatic injury or a surgical procedure. Within the internal pathway, factor IX is activated by factor IX and is upregulated by factor VIII. Once activated, factor IX then activates factor X in the common pathway. Activated factor X then activates and amplifies the common pathway's downstream components, leading to thrombin and fibrin formation. Without proper levels of factor IX, the cascade is unable to effectively activate factor X and thus affecting fibrin formation and predisposing to prolonged bleeding.[19]

Replacement of factor IX has evolved significantly over time. Originally in the 1950s and 1960s, either whole blood or fresh frozen plasma was used to replace factor IX. However, factor IX concentrations in these blood products were insufficient to stop serious bleeding and the use of allogeneic transfusions resulted in the transmission of viral diseases including HIV and hepatitis.[20] Subsequently, the development of novel plasma derived and recombinant factor IX preparations have allowed for the achievement of plasma concentrations high enough to prevent or stop bleeding as well as decreasing or eliminating the transmission of viral diseases. Alternatively, factor IX clotting factor concentrates that also contain factors II, VII, and X, known as prothrombin complex concentrates or recombinant factor VII, are available for specific indications in hemophilia B patients including patients who have developed inhibitors thereby limiting the efficacy of factor IX replacement therapy.[21] The World Federation of Hemophilia recommends the use of factor IX concentrates (plasma derived and recombinant) due to a reduced risk of thrombosis and disseminated intravascular coagulation compared to prothrombin complex concentrates. In addition to pure factor IX concentrates, adjuvants such tranexamic acid (TXA) can be used promote clot stability during surgical periods or following spontaneous bleeding episodes. In addition to factor replacement and use of coagulation adjuncts such as TXA, medications that may directly or indirectly impact coagulation function should be avoided. During the perioperative period, these include non-steroidal anti-inflammatory agents and synthetic colloids such as hydroxyethyl starches.

Dosing of factor IX concentrates takes into consideration the patient's starting factor IX level, the target factor IX level, and the specific product used (plasma derived or recombinant). With intermittent dosing, the dosing interval is based on the half-life of factor IX and its plasma clearance. For the majority of factor IX replacement products, the patient's factor IX level can be expected to increase by 1-1.4 IU/dL for each 1 unit/kg that is administered. This increase is less than that seen with factor VIII concentrates as the volume of distribution of factor IX is higher due to binding to the vascular endothelium and the lower molecular weight of factor IX which results in diffusion out of the vascular system into the interstitium. Given the potential for variations in plasma concentrations, monitoring plasma concentrations are recommended during therapy to ensure that therapeutic dosing is maintained. For our patient, a bolus dose was followed by a continuous infusion (BeneFIX, Pfizer, New York, NY) to ensure that a therapeutic plasma concentration was achieved and maintained.[17] A target factor IX level $\geq$ 80% of normal was chosen per national guidelines and recommendation from our pediatric hematology consultants. Prior to the start of the surgical procedure, this level was documented. Although there is limited evidence medicine to show its therapeutic superiority over intermittent dosing, the decision to use continuous factor IX infusion vs intermittent bolus infusions followed the World Federation of Hemophilia recommendations. Compared to intermittent bolus infusions, continuous infusions provide a constant steady-state that avoids the

potential for unsafe low trough levels or dangerously high peak concentrations.[22-24] Furthermore, there is a significant reduction in factor clearance compared to that of intermittent dosing with the potential to decrease total factor requirements by 30-40% when compared to intermittent dosing.[17,22]

In addition to monitoring routine coagulation function (PT, PTT, INR) and factor IX levels, we further assessed coagulation function intraoperatively by using rotational thromboelastometry (ROTEM®).[25] Commonly used laboratory coagulation measurements such as the INR, PT, and PTT do not capture the hemostatic process in real time, are unable to assess the quality or strength of the resultant clot, and do not evaluate the presence of fibrinolysis. As such, they may be more suitable for monitoring anticoagulation therapy as opposed to evaluating therapy for coagulation disturbances. Additionally, the turnaround time for these traditional measures may be prolonged. Both the TEG and ROTEM® are viscoelastic monitoring tools which rapidly provide a measure of whole blood clotting. These tests are performed by exerting a constant rotational force on a sample of blood and then monitoring its viscoelastic properties to determine clot formation (fibrin polymerization), clot strength, and clot degradation over time, thus evaluating both the intrinsic and extrinsic pathways of coagulation function.

Another important topic of discussion is the psychosocial aspect of an unforeseen hemophilia B diagnosis, especially prior to a major surgical procedure.[25] The impact of the new diagnosis was noted in our patient and psychology and social support provided. This was readily accepted by the family. A variety of studies have observed the impact of hemophilia B on a patient's everyday life.[26-29] These studies, mainly utilizing quality of life, functional involvement, and pain surveys, have demonstrated increased acute and chronic pain issues, an increased incidence of depression, and a significant impact on the patient's education, relationships, and physical activity.

In conclusion, we present a 13-year-old male with hemophilia B that was diagnosed during investigation of a prolonged APTT obtained on a routine preoperative laboratory evaluation. The diagnosis was achieved and appropriate perioperative interventions provided in a relatively asymptomatic patient whose diagnosis may have been missed had it not been for routine evaluation of coagulation function prior to a major surgical procedure. Our patient's case suggests the importance of routine screening of coagulation function prior to major surgical procedures as well as a thorough history as our patient did provide a history of bleeding after a tooth extraction. Perioperative care of patients with hemophilia B includes optimization of factor IX levels using plasma derived or recombinant factor IX along with adjunctive agents such as TXA. Additionally, avoidance of medications which impact coagulation function is mandatory.

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