Pediatric Anesthesia and Critical Care Journal 2025;13(1):34-40
doi:10.14587/paccj.2025.5

PACCJ

Perioperative care of an adolescent with factor XI deficiency during posterior spinal fusion

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Keypoints

1. Normal coagulation function requires the interplay of the vasculature including the endothelium with platelets and soluble coagulation factors including the intrinsic and extrinsic coagulation pathways.
2. Factor XI deficiency (Rosenthal disease or hemophilia C) is a rare autosomal recessive bleeding disorder with an incidence of 1:100,000. It is significantly less common than the X-linked disorders, hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency).
3. Clinical presentation generally includes the incidental identification of laboratory abnormalities during assessment of coagulation function or with bleeding following major surgical procedures or traumatic injury. Spontaneous hemorrhage is uncommon.
4. The mainstay therapies include replacement of the deficient factor with a factor XI concentrate or the use of fresh frozen plasma to correct FXI levels, with adjunctive antifibrinolytic therapies being indicated to decrease intraoperative blood loss. However, deficiency of factor XI is unique in that factor XI levels do not generally correlate with bleeding severity.
5. Use of the ROTEM® for continuous coagulation monitoring, specifically the monitoring of clot formation and dissolution kinetics, helps assess the quantitative response to plasma transfusions and the need for additional transfusions during the perioperative period.

Abstract

Factor XI (FXI) deficiency (Rosenthal disease or hemophilia C) is a uncommon autosomal recessive bleeding disorder. Clinical signs and symptoms of factor XI deficiency are generally limited; however, significant bleeding may occur following trauma or a surgical procedure. We present an adolescent with factor XI deficiency who presented for anesthetic care during posterior spinal fusion. The processes responsible for normal blood coagulation are presented, previous reports of perioperative care of patients with factor XI deficiency reviewed, and suggestions for perioperative care discussed.

Keywords

posterior spinal fusion; coagulation; factor XI; coagulation disturbances

Introduction

Normal coagulation function requires the interplay of the vasculature including the endothelium with platelets and soluble coagulation factors [1,2]. Following damage to the vascular endothelium, the first line of defense against bleeding is prostaglandin-mediated vasoconstriction. Platelet adhesion to the collagen-rich endothelium occurs via the interaction between von Willebrand factor and the

platelet glycoprotein Ib receptor. During platelet adhesion, the platelet glycoprotein IIb/IIIa receptor is activated, allowing for platelet aggregation with fibrinogen serving as the ligand. The conclusion of this primary hemostatic step is the formation of an initial platelet plug. Secondary hemostasis is classically described by the intrinsic and extrinsic coagulation pathways. Traditionally, the process of blood clotting has been presented in a series of discrete processes that include the intrinsic (contact activation), the extrinsic (tissue factor), and the common pathways. Although the description appears to suggest orderly, non-overlapping sequences, it fails to recognize the many interaction points between these pathways, the platelets, and endothelial cells.

The initiation of secondary hemostasis (coagulation cascade) occurs via the exposure of subendothelial tissue factor with binding and activation of factor VII which facilitates the formation of activated factor X in the extrinsic pathway. The conversion of prothrombin to thrombin in the common pathway occurs via activated factor X working in tandem with factor V, phospholipids, and calcium [2]. Prothrombin then acts to convert fibrinogen to fibrin, leading to formation of a clot to stop bleeding. The intrinsic pathway begins with the activation of factor XII through contact with a biologic or foreign surface. Factor XII activates factor XI which then activates factor IX. This results in the formation of active factor X through the common pathway [3].

Deficiency of a number of the soluble coagulation factors, most notably factors VIII (hemophilia A) or factor IX (hemophilia B or Christmas disease), can result in severe coagulation dysfunction resulting in life-threatening bleeding that may occur spontaneously or following minor trauma or surgical procedures. Less commonly, deficiencies of other soluble coagulation factors may manifest only as laboratory abnormalities during assessment of coagulation or with bleeding following major surgical procedures or traumatic injury. We present an adolescent with factor XI deficiency who presented for anesthetic care during posterior spinal fusion. The processes responsible for normal blood coagulation are presented, previous reports of perioperative care of patients with factor XI deficiency reviewed, and suggestions for perioperative care discussed.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital. The patient was a 15-year-old, 47.8 kg, adolescent male who presented for posterior spinal fusion from T2-L2 to treat congenital thoracic kyphoscoliosis with associated exaggerated thoracolumbar lordosis. Imaging confirmed the presence of kyphoscoliosis with hemivertebra at T6 and T7. The patient's past medical history was positive for factor XI deficiency, diagnosed at 15 years of age via factor XI gene testing due to presentation of easy bruising and a prolonged partial thromboplastin time (PTT). He had also been diagnosed with a bicuspid aortic valve, asthma, and allergic rhinitis. There was no prior surgical history. His medications at the time of surgery included cholecalciferol (Vitamin D3, 1250 µg PO every day), tranexamic acid (1300 mg PO PRN) to control bleeding, mometasone-formoterol aerosol inhaler (2 puffs TID), fluticasone propionate nasal spray, cetirizine (10 mg PO every day), and albuterol inhaler (2 puffs every 4 hours PRN). Physical examination revealed a thin adolescent male in the 4th percentile for height and 5th percentile for weight. His airway examination revealed a Mallampati Class II airway with a thyromental distance greater than three fingerbreadths. His vital signs and cardiorespiratory examination were unremarkable. A preoperative factor XI level was 31-33%. Given the factor XI deficiency diagnosis, after consultation with the pediatric hematology service, it was recommended that factor XI be maintained at ≥ 50% during and immediately after the procedure. On the morning of surgery, 5 mL/kg of fresh frozen plasma (FFP) was administered and additional doses of FFP were planned as needed intraoperatively to maintain normal coagulation function and the factor XI level.

Preoperative medications included aprepitant (40 mg PO), scopolamine transdermal patch, and gabapentin (600 mg PO). Perioperative *in vivo* coagulation function was monitored using the rotational thromboelastogram (ROTEM®). The patient was kept *nil per os* for 6 hours and transported to the operating room. Routine American Society of Anesthesiologists monitors were placed followed by the induction of anesthesia via inhalation of incremental concentrations of sevoflurane in air and oxygen. A peripheral intravenous cannula was placed followed by the administration of propofol (200 mg) and lidocaine (40 mg). Rocuronium (50 mg) was administered to facilitate endotracheal intubation with a 7.0 mm cuffed ETT using direct laryngoscopy. A second peripheral intravenous cannula and an arterial cannula (radial artery) were placed. The patient was turned prone on the operating room table and positioned with pressure points padded. To facilitate neurophysiological monitoring per our usual protocol, maintenance anesthesia included desflurane titrated to maintain the bispectral index at 50-60, a remimazolam infusion (3-10 µg/kg/min), methadone (5 mg), and a remifentanil infusion (0.1-0.3 µg/kg/min) to maintain the mean arterial pressure at 55-65 mmHg [4]. Tranexamic acid was administered as a bolus dose of 50 mg/kg followed by a continuous infusion at 5 mg/kg/hr. Maintenance anesthesia was supplemented by a continuous infusion of lidocaine (1 mg/kg/hr). Cefazolin (2000 mg) was administered every 3 hours for prophylaxis against surgical site infection. Intraoperative clevidipine was used to maintain the mean arterial pressure at 55-65 mmHg to limit intraoperative blood loss, and intraoperative blood salvage used to limit the need for allogeneic blood products. The ROTEM® was used intraoperatively to monitor coagulation function, and remained at baseline except for a mild increase in the clot formation time (CFT). No intraoperative FFP or allogenic blood products transfusions were administered. The surgical procedure lasted 6 hours 40 minutes. Estimated blood loss was 200 mL and urine output was 551 mL. Intraoperative fluid intake included 500 mL of 2% buffered saline and 2048 mL of Normosol®-R electrolyte solution. Prophylaxis against postoperative nausea and vomiting included ondansetron (4 mg). At the completion of the surgical procedure, the patient was turned supine, his trachea extubated, and he was transported to the post-anesthesia care unit. Postoperative pain management included intravenous acetaminophen every 6 hours and hydromorphone delivered via a patient-controlled analgesia device. On the evening following surgery, he received a single dose of 5 mL/kg of FFP to maintain the factor XI level ≥ 50%. On postoperative days 1 and 2, he received additional transfusions of FFP. The factor XI level was 49% on postoperative day 3 and no additional FFP was administered. The factor XI level decreased to 40% on postoperative day 4 and FFP was administered. On postoperative day 5, his factor XI level was 49% and he was discharged home with follow-up to the hematology infusion clinic scheduled for the first two days after discharge. On postoperative day 10, he was admitted to the emergency department for evaluation of dizziness with leg weakness and paresthesia in the lower extremity. His factor XI level was 31% and FFP was administered. Computed tomography of the thoracolumbar spine demonstrated an epidural hematoma from T8 to T12 along the dorsal and left lateral thecal sac with mild anterior displacement of the thecal sac and cord. The cord preserved normal caliber. The findings were confirmed by MR imaging. Following admission, his neurologic examination was stable. The following day, his factor XI level was 44% and FFP was administered. Due to improvement of paresthesia, he was discharged home. There was continued improvement of his clinical symptoms with resolution of the neurologic changes. The remainder of his postoperative course was unremarkable, with his 14-day postoperative factor XI level being 55%.

Discussion

Factor XI (FXI) deficiency, Rosenthal disease or hemophilia C, is a rare autosomal recessive bleeding disorder with an incidence of 1:100,000. It is less common than

the X-linked disorders, hemophilia A (factor VIII deficiency) with an incidence of 1:5000 male births and hemophilia B (factor IX deficiency) with an incidence of 1 in 25,000 [5]. The responsible gene is located on chromosome 4, with 152 mutations having been identified [6]. Although the degree of factor XI deficiency appears to be associated with the number of affected alleles, even the most severe deficiency rarely results in spontaneous bleeding. The clinical signs and symptoms of factor XI deficiency are generally limited with a low risk of spontaneous bleeding. It is most often diagnosed when prolonged bleeding occurs following trauma or surgery, or when a prolonged PTT is incidentally noted during preoperative evaluation of coagulation dysfunction [7,8]. First discovered in 1953 by Rosenthal et al., plasma thromboplastin antecedent (PTA) or FXI deficiency was identified in a longitudinal study of three family members [9]. The patients of interest exhibited no distinct clinical symptoms outside of the mild hemorrhage experienced when undergoing tooth extractions. It was confirmed that the three family members had a similar clotting defect when their plasma did not correct each other's laboratory coagulation abnormalities. The plasma clotting time and serum prothrombin time were compared to two patients with known hemophilia A and hemophilia C, and it was found that their clotting times were mildly prolonged. Additionally, they made the clinical distinction that FXI deficiency is inherited and can occur in both sexes [9]. While FXI is necessary for normal coagulation in *in vitro* systems, individuals with FXI deficiency have a variable bleeding risk that cannot be predicted from the FXI antigen [1]. Bleeding is most often trauma related, especially in the nose, genitourinary tract, and oral mucosa, where high fibrinolytic activity is present [10]. Preoperative laboratory tests often incidentally discover FXI deficiency when a prolonged activated PTT (aPTT) is present with a normal platelet count and fibrinogen concentration. After the identification of prolonged aPTT, FXI gene testing is used to confirm the diagnosis. In a case series performed by Singh et al, diagnosis of FXI deficiency was based on either a family history of FXI deficiency or prior intraoperative bleeding [11]. Therefore, a patient's trauma history and family history in addition to FXI levels and aPTT are crucial for FXI deficiency diagnosis and the guidance of treatment for surgical interventions. In our patient, a history of easy bruising and a prolonged aPTT led to the diagnosis of FXI deficiency following FXI gene testing.

There are a limited number of reports in the literature regarding the perioperative care of patients with FXI deficiency (Table 1) [6,10,12-20]. The primary therapies include replacement of the deficient factor with a FXI concentrate or FFP. Obtaining concentrated FXI is expensive, difficult, and has been associated with a high risk of thrombosis. Because of this, treatment includes the administration of FFP based on serial FXI levels with a goal to maintain the FXI level ≥ 40-50% (40-50 IU/dL) for major surgical interventions. These levels are generally associated with a normal coagulation panel (aPTT). While FFP is more readily available, it is associated with an increased risk of transmitted infections, volume overload, and allergic reactions [12,21]. As the half-life of factor XI is 60-80 hours, factor levels can be monitored every 24 hours with FFP being administered every 24-72 hours. Although we used intermittent dosing, when there is a severe risk of bleeding or ongoing hemorrhage, a continuous infusion of FFP has been used.

Although FFP remains the primary treatment, adjunctive therapies include anti-fibrinolytics (aminocaproic acid, desmopressin or tranexamic acid), or recombinant factor VIIa [10,20-21]. Based on our patient's response to FFP, the intended surgical procedure, and the severity of his FXI deficiency, we chose to use tranexamic acid to augment coagulation function during the surgical procedure. Tranexamic acid (TXA), a lysine derivative, blocks plasminogen conversion to plasmin, inhibiting fibrinolysis and stabilizing the fibrin meshwork in secondary hemostasis. When compared to aminocaproic acid, TXA has a

Author and Reference	*Patient demographics and surgical procedure*	*Perioperative coagulation care*
Adibelli B et al [6].	59-year-old woman for left total hip arthroplasty.	FFP and RBC. Coagulation function monitored via aPTT.
Dirkmann D et al [10].	5-year-old girl for elective adenoidectomy and tympanoplasty.	Intravenous tranexamic acid (15 mg/kg). Coagulation function monitored with ROTEM®. Postoperative oral tranexamic acid for 8 days.
Burgos Pratx LD et al [12].	54-year-old man for open extended right hepatectomy for liver metastases.	Preoperative TEG with FFP. Intravenous tranexamic acid. Coagulation function monitored with ROTEM®. Postoperative FFP. Preoperative and postoperative PT and aPTT monitored.
Fitzsimons MG et al [13].	62-year-old man for sternotomy for repair of an ascending aorta aneurysm and aortic valve replacement.	FFP, intravenous aminocaproic acid, cell-saver. Postoperative FFP, intravenous aminocaproic acid for 72 hours. Coagulation function monitored via aPTT and PT.
Ince ME et al [14].	68-year-old man for coronary artery bypass graft surgery.	FFP, RBC, intravenous tranexamic acid, and platelet suspension. Coagulation function monitored via aPTT.
Petroulaki A et al [15].	73-year-old woman for aortic valve replacement with cardiopulmonary bypass.	Preoperative and postoperative FXI concentrate. Intraoperative RBC, FFP, platelets, cell-saver, and tranexamic acid.
Seriyaku H et al [16].	66-year-old man for laminoplasty at C3-C6	Preoperative and intraoperative FFP. Coagulation function monitored via aPTT.
Yamada Y et al [17].	85-year-old male for bipolar hip arthroplasty.	Perioperative FFP. Coagulation function monitored via aPTT. Postoperative FFP and RBC.
Kato T et al [18].	43-year-old man for teeth extraction.	Perioperative FFP. After maxillary teeth extraction, pressure hemostasis and tranexamic acid. After mandibular tooth extraction, coagulation achieved via carbon dioxide laser.
Lee SE et al [19].	25-year-old woman for Le Fort I osteotomy and bilateral sagittal split osteotomy.	Intraoperative FFP and autologous blood. Coagulation function monitored with ROTEM®.
Kazui T et al [20].	76-year-old man for cardiopulmonary bypass.	Perioperative FFP. Intraoperative aminocaproic acid, heparin. Coagulation function monitored with ROTEM®.

Table 1. Previous reports of anesthetic care in patients with factor XI deficiency. FFP = fresh frozen plasma; RBC= packed red blood cells; TEG=thromboelastogram; ROTEM®=rotational thromboelastogram; aPTT= activated partial thromboplastin time; PT= prothrombin time.

binding affinity to plasminogen that is almost 10 times more potent. With its broad applications and limited adverse effect profile, TXA has been used during various surgical interventions in patients with inherited or acquired coagulation dysfunction [22,23].

Upon review of previous reports of anesthetic care in patients with Factor XI deficiency, coagulation function has been monitored using routine laboratory parameters (aPTT), factor XI levels, and point-of-care coagulation testing such as the thromboelastogram (TEG), or the ROTEM® [6,10,12-20]. Since routine laboratory parameters of coagulation function (PT and PTT) do not adequately assess platelet function, are normalized with factor XI levels ≥25-30%, and do not reflect the clinical interplay of the various components of the coagulation cascade, we utilized ROTEM® to evaluate and monitor *in vivo* coagulation function in our patient [24]. Due to adequate intraoperative coagulation function as demonstrated by the ROTEM®, no intraoperative FFP was given. Postoperatively, quantitative factor levels were monitored and FFP administered on days 1, 2, and 4 to maintain factor XI levels within the desired range of ≥ 40%.

ROTEM® and TEG are ideal for the continual monitoring of blood clot kinetics in patients with hemostatic defects due to their ability to rapidly return data, allowing for their use in goal-orientated hemostatic therapies. We utilized the ROTEM® data to quantitatively assess the patient's response to FFP transfusions, tranexamic acid, and transfusion requirements throughout the perioperative period. Despite this care, there was unexpected postoperative bleeding into the epidural space resulting in spinal cord irritation with clinical neurologic changes prompting readmission to the hospital. Fortunately, observation demonstrated no expansion of the epidural bleeding and the patient was successfully discharged home without additional surgical intervention.

In summary, we describe the perioperative care of an adolescent with factor XI deficiency undergoing posterior spinal fusion for congenital thoracolumbar kyphoscoliosis. Perioperative discussion and planning included the hematology service, surgical team, and anesthesia care providers. While fresh frozen plasma transfusions remain the first-line treatment for bleeding prevention and management, we highlight the utility of tranexamic acid as an effective adjunctive antifibrinolytic agent. This case

contributes to the literature by demonstrating the benefits of ROTEM® for continuous coagulation monitoring in this unique scenario.

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