A Jehovah's Witness child with hemophilia B and factor IX inhibitors undergoing scoliosis surgery

[Chirurgie de la scoliose chez un enfant Témoin de Jéhovah souffrant d'hémophilie B et présentant des inhibiteurs du facteur IX]

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Purpose: To describe the successful perioperative hemostatic management of a Jehovah's Witness patient with hemophilia B and anaphylactic inhibitors to factor IX, undergoing scoliosis surgery.

Clinical features: A 14 ½-yr-old boy with severe hemophilia B who had a history of anaphylactic inhibitors to factor IX was scheduled to undergo corrective scoliosis surgery. He was initially started on epoetin alfa and iron supplementation to maximize preoperative red cell mass. Additionally, he was placed on a desensitization protocol of recombinant coagulation factor IX (rFIX) and was then treated with activated recombinant coagulation factor VII (rFVIIa) during the postoperative period. Tranexamic acid was given concomitantly. The intraoperative blood loss was approximately 350 mL. The nadir hemoglobin concentration was 111 g·L⁻¹ on postoperative days one and two. On postoperative day 11, the patient was stable and discharged home with a hemoglobin of 138 g·L⁻¹. He did not require blood transfusion and no adverse events were observed.

Conclusions: The use of rFIX, rFVIIa, erythropoietin, iron, and tranexamic acid before, during and after scoliosis surgery may be a viable and safe option for hemophilia patients with inhibitors, who refuse blood products.

d'inhibiteurs anaphylactiques du facteur IX devait subir une chirurgie de correction de scoliose. On lui a d'abord administré de l'époétine alpha et des suppléments de fer pour maximiser la masse érythrocytaire avant l'opération. De plus, il a reçu un traitement de désensibilisation à l'aide de facteur IX recombinant (rFIX), puis a été traité avec du facteur VII recombinant activé (rFVIIa) après l'opération. Il a simultanément reçu de l'acide tranexamique. Les pertes sanguines peropératoires étaient d'environ 350 mL. La concentration d'hémoglobine a atteint un minimum de 111 g·L⁻¹ les premier et deuxième jours après l'opération. Le onzième jour postopératoire, le patient était stable et a pu recevoir son congé de l'hôpital. Son hémoglobine était alors 138 g·L⁻¹. Il n'a pas nécessité de transfusion sanguine et il n'y a pas eu d'événements indésirables.

Conclusion : L'administration de rFIX, de rFVIIa, d'érythropoïétine, de fer et d'acide tranexamique avant, pendant et après une chirurgie de correction de scoliose pourrait constituer une option viable et sécuritaire pour les patients hémophiles présentant des inhibiteurs et refusant la transfusion de produits sanguins.

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Objectif : Décrire la prise en charge hémostatique périopératoire réussie d'un patient Témoin de Jéhovah souffrant d'hémophilie de type B et présentant des inhibiteurs anaphylactiques de forte teneur du facteur IX, lors d'une chirurgie de la scoliose.

Éléments cliniques : Un garçon de 14 ans et demi souffrant d'hémophilie de type B et présentant des antécédents

HEMOPHILIA B is an X-linked, recessive hemorrhagic disorder characterized by a deficiency of factor IX clotting activity. Sometimes referred to as Christmas disease, it occurs in approximately one in 25,000 to 30,000 male births.¹ Treatment of hemophilia B typically requires supplementing the patient with the deficient clotting factor. However, replacement therapy may be complicated by the appearance of an inhibitor against the administered factor in 3-5% of the

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patients.² This represents the greatest complication in replacement therapy and has rendered the treatment of hemophilia less straightforward.³ Anaphylaxis develops contemporaneously with the appearance of inhibitor in half of these patients.²

Although the frequency of spontaneous bleeding is not necessarily increased in patients with inhibitors, the level of the inhibitor and the magnitude of the individual's anamnestic response to factor challenge dictate the outcome of hemostasis.³ Good control of hemostasis is particularly important in patients with inhibitors who are scheduled for surgery.

Individuals of the Jehovah's Witness (JW) faith often refuse blood products for religious reasons. Maintaining hemostasis during surgery in a hemophilic patient with inhibitor who refuses blood derived products can be challenging. Fortunately, strategies have been developed to maximize blood conservation and minimize the need for blood transfusion.

We describe a case of successful perioperative hemostatic management for scoliosis surgery in a 14 ½-yr-old JW boy with severe hemophilia B who had a history of anaphylactic inhibitors to factor IX. Consent for publication was obtained verbally from parents and patient according to guidelines of the British Columbia Children's Hospital. Institutional approval for publication was also obtained.

Case report

The patient was diagnosed with factor IX deficiency when he presented initially at 20 months of age with an internal hemorrhage in his calf. He was subsequently diagnosed to have severe factor IX deficiency. His other health concerns included growth hormone deficiency, hypothyroidism, occasional reactive airways disease, learning difficulty, and seizure disorder, none of which was thought to be related to his bleeding disorder. His medical conditions were controlled with numerous medications including clobazam, phenytoin, levothyroxine, salbutamol, multivitamins with iron, and growth hormone injections.

Following his initial presentation the patient had multiple bleeding episodes including three hemarthroses of his right knee, a significant subcutaneous hematoma of his arm, a left-sided groin bleed, and a significant right elbow bleed. None of these hemorrhagic episodes was treated with factor IX concentrate, because the family resisted the use of plasma-derived factors due to religious convictions.

With the introduction of recombinant factor IX concentrate (rFIX), however, the patient started using rFIX infusions. At age ten he received two infusions of rFIX for two episodes of right-sided thigh bleed-

ing. During the same year, he presented again with a significant lower limb bleed and was given a third rFIX infusion. Shortly after the third infusion, he began coughing, gagging, and retching and became cyanotic and diaphoretic. A severe allergic reaction was diagnosed, the infusion was stopped and intravenous diphenhydramine was administered. He recovered rapidly without the use of epinephrine or corticosteroids. As a result of his anaphylactic reaction, no further doses of rFIX were given. A skin test was positive to rFIX. Serum testing revealed that he had an immediately acting inhibitor with a level of 2.5 Bethesda units per millilitre (BU·mL⁻¹).

As a result of the presence of inhibitor, he was started on activated recombinant human blood coagulation factor VII (rFVIIa) for on-demand hemostasis management. During the same year in which the patient developed inhibitor to rFIX, he was diagnosed with juvenile onset idiopathic scoliosis and he started wearing a back brace. He was scheduled to undergo corrective surgery at age 12. After a trial of the factor IX desensitization protocol, surgical plans were postponed as his spinal curvature was deemed to have been stable. At age 13 he received a general anesthetic for a radiofrequency ablative synovectomy, uneventfully, with rFVIIa coverage. At age 14 the spinal curvature had increased to an angle of 65–70° and scoliosis surgery was again scheduled.

Prior to surgery, the surgeon consulted with the family and the church elders. All parties agreed to seek a route that would minimize the possibilities of philosophical beliefs coming into conflict. In addition to hematological strategies to maximize preoperative hemoglobin and minimize blood loss, the surgeon agreed to terminate the procedure should a trend in blood loss occur that might necessitate blood product transfusion and to consider transfusion only in the event of a life-threatening blood loss. The agreement was documented in the patient's record. The parents were not required to sign a transfusion consent form.

A set of procedures and protocols were used to optimize preoperative hemoglobin concentration, ensure adequate perioperative hemostasis and limit blood loss. These procedures included the use of preoperative blood augmentation with erythropoietin 300 U·kg⁻¹ three times a week, and oral iron syrup (Palafer®) at a dose of 5 mL *tid*, three weeks prior to surgery. Two days prior to surgery, laboratory investigation revealed a markedly elevated activated partial thromboplastin time (APTT), and slight elevations of the prothrombin time (PT) and international normalized ratio (INR) (Table). Desensitization was initiated at this time with rFIX 120 U·kg⁻¹ under coverage of

TABLE Laboratory values

<i>Test results (normal ranges)</i>	<i>Two days prior to surgery</i>	<i>Preoperative</i>	<i>Intraoperative</i>	<i>Postoperative day one</i>
PT (sec) (10.1-12.0)	12.4	12.1	12.1	12.2
INR (0.91-1.10)	1.14	1.1	1.1	1.12
APTT (sec) (26.7-35.3)	94.3	28.2	28.7	31.8
Hgb (g·L ⁻¹) (125-165)	127	149	138	111
Plt (·L ⁻¹) (180-440) x10 ⁹	196	203	210	194
Ferritin (ug·L ⁻¹) (29-84)	452	n/a	n/a	n/a
Factor IX (0.77-1.38)	0.66	1.05	1.03	0.49
Factor IX Inhibitor (BU·mL ⁻¹)	n/a	0.20	n/a	n/a

*n/a = laboratory data not available. PT = prothrombin time; INR = international normalized ratio; APTT = activated partial thromboplastin time; Hgb = hemoglobin; Plt = platelet count.

diphenhydramine and hydrocortisone. Tolerance was maintained using rFIX every 12 hr. Preoperatively, the hemoglobin (Hgb) concentration was 149 g·L⁻¹. PT, INR, and APTT values were 12.1 sec, 1.11 sec and 28.2 sec respectively. The Factor IX level was > 100% and factor IX inhibitor level was 0.20 BU·mL⁻¹.

On the morning of surgery, rFIX 120 U·kg⁻¹ was given preoperatively. Following induction of general anesthesia a right internal jugular, arterial, and two large bore peripheral intravenous catheters were inserted. Prior to incision a bolus of tranexamic acid (10 mg·kg⁻¹ *iv*) was given followed by an infusion at 2 mg·kg⁻¹·hr⁻¹. Total surgical time was four hours for posterior spinal fusion from the levels T2–L1. Surgical hemostasis was facilitated by local infiltration with 1:500,000 epinephrine, monopolar cautery, and the use of an argon gas coagulator. The intraoperative blood loss was approximately 350 mL (12% of total blood volume) and total intravenous fluid administered was 2700 mL. Immediately after surgery, the patient's Hgb was 138 g·L⁻¹ and PT, INR and APTT values were 12.1 sec, 1.1 sec, and 28.7 sec respectively. No blood was transfused.

The patient's trachea was extubated postoperatively shortly after rFIX infusion. He received morphine by patient-controlled analgesia, midazolam *prn*, and continued with an rFIX infusion, tranexamic acid, erythropoietin and rFVIIa. Diphenhydramine 50 mg *iv* and hydrocortisone 50 mg *iv* were given prior to each dose of rFIX. Activated partial thromboplastin times were monitored daily to assess the adequacy of factor IX levels.

On postoperative day (POD) three, erythropoietin was discontinued and oral iron was restarted to ensure adequate iron replacement of the perioperative blood loss. The patient continued to receive rFIX with hydrocortisone and diphenhydramine coverage. On POD four, the patient's APTT increased abruptly, signalling the onset of an anamnestic FIX inhibitor. From that point onwards, intravenous rFVIIa 4.8 mg (approximately 100 µg·kg⁻¹) q4h was prescribed, rather than rFIX. Tranexamic acid (1 g *po* q8h) was administered for two weeks post-surgery to ensure adequate wound healing before clot lysis. The post-operative factor IX levels, PT, INR and APTT values are displayed in the Table. On POD 11, the patient was stable and discharged home with a Hgb of 138 g·L⁻¹. No adverse events were observed. A follow-up appointment one week after discharge revealed a serum factor IX level of 160 BU·mL⁻¹.

Discussion

If left untreated, patients with hemophilia B may experience approximately two to five spontaneous bleeding episodes per month.⁴ The clinical severity of bleeding episodes is usually correlated with factor IX coagulant activity.

The mainstay of hemostatic treatment of hemophilia B is the replacement of factor IX. However, approximately 3 to 5% of patients with severe hemophilia B will develop inhibitor antibodies after receiving replacement therapy, rendering further replacement therapy ineffective.^{5,6} The median number of factor exposure days prior to inhibitor detection is between 9 and 12.⁵

Testing should be carried out before any elective surgery or emergency surgery.³ Annual inhibitor screening should be done as part of the comprehensive care for hemophilia patients. Screening was not done prior to the anaphylactic episode in our patient as he was unable to attend the hemophilia clinic.

Despite the presence of inhibitors, the frequency of bleeding may not be increased. However, hemostasis is extremely difficult to control in patients with high responding inhibitors. In individuals with low inhibitor titre ($< 5 \text{ BU} \cdot \text{mL}^{-1}$), hemostasis can be achieved by administering a high dose of factor concentrate to “overwhelm” the inhibitor. However, this is difficult if the patient develops anaphylaxis to factor IX administration. An alternate treatment is the use of plasma derived factor VIII inhibitor bypassing activity (FEIBA), an activated prothrombin concentrate containing activated clotting factors which can achieve hemostasis by “bypassing” the need for both factors IX and VIII to generate thrombin. The factor IX contained in FEIBA could again cause anaphylaxis, and promotes an anamnestic response. Furthermore, the religious convictions of the family would have prohibited the use of this plasma derived factor product.

Recombinant factor VIIa is the agent of choice for hemostatic management for hemophilia B inhibitor patients, especially in children. It is a recombinant product free from the risks of blood borne pathogens, and was deemed acceptable to this family. As early as 1988, Hedner *et al.*⁷ reported the successful use of rFVIIa for open knee synovectomy in a hemophilia patient with a FVIII inhibitor. There is also support for the use of rFVIIa in providing hemostatic prophylaxis for central catheter insertion.⁵ The recommended dose is $90 \text{ ug} \cdot \text{kg}^{-1}$.⁸ The *in vivo* half life of rFVIIa is about two hours but is shorter in children than in adults. With this patient being in his mid-teens, we were confident that dosing in the higher recommended range every two hours would be adequate to achieve postoperative hemostasis. Continuous infusion after an initial bolus dose has provided adequate surgical coverage and control of bleeding episodes to a small number of inhibitor patients, although failures have also been reported.⁶ Development of antibodies to this agent is not a clinical concern except in patients with factor VII deficiency.⁶ However, a disadvantage of using rFVIIa is the lack of a relevant laboratory test to guide dosage during the critical immediate postoperative phase in this hemostatically challenging surgery. In view of this fact, and the low preoperative inhibitor titre, we employed an alternative means of hemostatic treatment. We desensitized our patient in the short term, and used high doses of factor IX

concentrate to achieve a therapeutic factor IX level. We anticipated a return of the anamnestic antibody response within several days. We used a generic protocol for desensitization over a three-hour period under the cover of antihistamine and corticosteroid, to give the patient high dose factor IX without significant anaphylactic reaction.⁹ In the first few postoperative days, APTT was monitored frequently, knowing that values would be increased once the anamnestic antibody had set in. Confirmatory factor IX levels were monitored on a daily basis. We planned to switch our patient to rFVIIa once the APTT became prolonged (confirmed by a low or absent FIX level) to ensure postoperative hemostatic control. By so doing, we optimized the immediate postoperative hemostasis in a patient with strong opposition to blood transfusion, in a cost-effective manner. The use of a fibrinolytic inhibitor in conjunction with rFVIIa can further safeguard the achievement of hemostasis in major surgeries. This is especially so in children where the risk of thrombosis is small.¹⁰

The fact that JW patients refuse the use of blood and blood products represents a challenge in optimal hemostatic management. A plethora of ethical, psychological, and legal issues revolve around the medical treatment of JW patients when the medical good is seen to be preeminent. In the case of this pediatric patient, the parents were not required to sign a consent form for blood transfusion, and the surgeon and family wished to avoid apprehension either preemptively or in the event of catastrophic blood loss. Prior to surgery, the parents, patient and surgical team all understood that a blood transfusion would be ordered by the surgeon in consultation with the attending anesthesiologist only if that transfusion was required to respond to life-threatening bleeding that directly resulted from the surgical act. Discussion with a Canadian Medical Protective Association legal representative followed, and confirmed that written documentation of the collective understanding between the parents, patient, anesthesiologist and surgeon was acceptable as informed consent. By framing the discussion to concentrate on the overarching philosophies of life or “world view” of all parties and making secondary the “medical good”, the parents and patient were willing to proceed and respect the surgeon’s religious beliefs without denying their own. Thus, a negotiated “beneficence-in-trust” was achieved that was acceptable to all parties without resorting to a legal confrontation.¹¹

In conclusion, hemostatic management for a child with hemophilia with anaphylactic inhibitors during surgery is difficult. In patients who cannot accept

autologous blood transfusion due to religious convictions, hemostatic management may be challenging. Using a combination of protocols including the use of medications such as rFIX, rFVIIa, erythropoietin, iron, and tranexamic acid before, during and after the operation, anesthesia and surgery proceeded safely for this patient. The operation was successful, there was minimal blood loss, and the patient recovered uneventfully.

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