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Management of Surgical Patients With Bleeding Disorders

ABSTRACT

Invasive procedures for patients with bleeding disorders require planning on the part of the health care team. The patient population affected involves those with hereditary bleeding disorders, such as von Willebrand disease or hemophilia; in addition, patients who use antithrombotic drugs must be considered and their care managed. The choice of treatment depends on a number of factors, including the procedure planned, the type and severity of the disorder, and the age and morbidity of the patient. The indications, dosing, and timing of presurgical and surgical interventions will be reviewed, as well as special considerations for vascular access devices.

Key words: bleeding disorder, factor, hemophilia, infusion, inhibitors, surgery, thrombosis, von Willebrand diseases

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There are no factor products currently approved for use in continuous infusion; however, the use of continuous infusion of factor is widely reported in the literature.

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Hemophilia and von Willebrand disease (vWD) are genetic conditions that lead to prolonged bleeding with surgical and dental procedures and injury. Hemophilia A, or factor VIII deficiency, is the most common genetic bleeding disorder (BDO), with a prevalence of 1 in 5000 male births. Hemophilia B, also known as factor IX deficiency, is much less common, occurring in just 1 in 25 000 male births. Hemophilia is an X-linked recessive disorder primarily affecting males, although females who are carriers may have a milder version of the BDO.[1] vWD (a deficiency or dysfunction of von Willebrand factor) is an autosomal dominant condition, affecting men and women equally, that has as its most common manifestation mucous membrane bleeding.[2] BDOs are generally classified as mild, moderate, or severe according to the person's native factor level (Table 1).

Surgical procedures can be performed safely in people with BDOs, despite their genetic tendency toward prolonged bleeding, with treatment tailored to the BDO and the type of surgery needed. With the availability of safe and effective treatment products, and with a well-thought-out treatment plan, peri- and postoperative bleeding complications can be prevented in most cases.

The variety of surgical procedures performed on people with BDOs is extensive and includes placement of central venous access devices (CVADs); dental extractions and other procedures; ear, nose, and throat surgeries (such as tonsillectomy, adenoidectomy, and insertion of myringotomy tubes); orthopedic surgeries; circumcision; and many others.[1,3] There are case studies in the literature of many types of procedures that have been performed on patients with BDOs, including abdominal, urologic, cardiac, and gynecologic surgeries.

In this article, historical context for the surgical care of patients with BDOs will be provided, along with discussion about available treatment products and consideration for their use in preventing intra- and postoperative bleeding. A team approach is needed to manage surgery in BDO patients, and team members' roles will be outlined with an emphasis on the infusion nurse's role.

TABLE 1

Severity of Hemophilia Based on Factor Levels

Factor Level	Classification	Bleeding Symptoms	Frequency of Treatment
>50%	Normal	Normal	None
6%-49%	Mild	With surgery, tooth extractions, major injury	Infrequent factor use
1%-5%	Moderate	With surgery, dental procedures, moderate injury. May develop hemophilic joint disease.	Frequent; may use factor prophylaxis
<1%	Severe	Frequent bleeding with minimal injury. Joint and muscle bleeds common; may have joint disease.	Factor prophylaxis recommended

HISTORICAL PERSPECTIVE ON SURGERY FOR HEMOPHILIA PATIENTS

Historically, people with BDOs have not tolerated surgical procedures well. Early rabbinic writings recognized a genetic cause for prolonged postsurgical bleeding and allowed a child to avoid circumcision if his mother had previously had 2 male children die following the procedure.

In 1935, Friedrich, a German physician, wrote a review of surgery in hemophilia which reported that surgery for hemophiliacs was so difficult that it was often postponed until the patient was close to death. Half of the patients in his reported cases bled to death postoperatively. Tavernier wrote in 1938 that blood transfusion could be used to control hemorrhage and replace blood loss, but hemorrhagic mortality remained at least 25%.[4]

It was not until the 1960s that new techniques were developed that allowed for fractionation of plasma products, with fraction I, or Cohn's fraction, having the ability to provide improved hemostasis. With this new product, hemorrhagic mortality declined to 10%. The discovery of the process for cryoprecipitation by Judith Graham Pool, MD, revolutionized surgical care for people with hemophilia. Treatment with cryoprecipitate allowed for elective surgical procedures, but 11% of patients continued to have major surgical bleeding, and 2% of all hemophilia surgical patients bled to death.[4]

The advent of factor concentrate products in the late 1960s and early 1970s, which allowed for replacement of factor VIII and factor IX, made it possible for hematologists to prescribe treatment that nearly normalized the coagulation profile for people with BDOs. Target factor levels could be established and achieved, and in the absence of inhibitors, a person with a BDO could experience the advantages of modern surgical therapy.

TREATMENT TO PREVENT BLEEDING WITH SURGICAL PROCEDURES

The imperative for establishing effective hemostasis and preventing peri- and postoperative bleeding in people with BDOs exists for many reasons. One goal is to prevent exsanguination with surgical procedures, and bleeding that occurs without threat of death has the potential to slow wound healing and to cause many postoperative complications. For these reasons, the goal of effective coagulation during and after surgery is to produce the best outcomes for patients with BDOs.

Optimal surgical wound healing requires effective hemostasis.[5] Normal wound healing takes place in 4 phases: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) remodeling.[6] The hemostatic phase begins as soon as the wound occurs, and effective hemostasis sets the stage for the subsequent phases of healing. The process of coagulation releases growth factors and other biologically active molecules that help with healing and the inflammatory response.[6] A stable blood clot provides the framework on which postoperative tissue repair takes place. Inadequate postsurgical hemostasis may cause complications, such as hematomas, infection, skin necrosis, and dehiscence. The duration of treatment required to support postoperative hemostasis in patients with BDOs ranges from 5 days to 4 weeks, depending on the type and severity of the BDO and the surgical procedure being treated.

Although many treatment options are available today to prevent bleeding during surgical procedures among those with BDOs, there are few widely adopted best-practice protocols. Options include bolus dosing of factor replacement products versus continuous infusion; the use of desmopressin as a treatment option for some diagnoses; outpatient versus inpatient care; laboratory monitoring of factor levels and response to treatment; the use of adjuvant medications, such as antifibrinolytics; and the application of topical products to help with

clotting.[3] Treatment plans are individualized and based on the severity of the BDO, the patient's historical response to treatment, the complexity of the surgical procedure, and available resources.[7]

FACTOR REPLACEMENT

Replacement coagulation factor products currently available for treatment of the most common BDOs (hemophilia A, hemophilia B, and vWD) are widely available in the developed world. The products are effective in preventing and treating bleeding, and have established safety records. Factor replacement products may be made from human plasma or be laboratory derived using recombinant technology. Provided in lyopholized powder form, with the appropriate diluent and mixing device, they are given intravenously and are dosed according to the weight of the patient and the target factor level.[8]

Having a good understanding of the half-life of treatment products for the prevention of perioperative bleeding in patients with BDOs is critical in creating a treatment plan. Infused factor VIII is expected to have an average half-life of 8 to 12 hours. Factor IX products have a longer half-life of 16 to 20 hours.[9] Factor half-lives are briefer in children,[3] which is why many pediatric hematology teams conduct pharmacokinetic (PK) studies before major surgical procedures.[7] PK studies may be as simple as a trough and peak drawn before and after a standardized dose, or more complex. Shapiro et al[10] describe a practical method for obtaining PK data in individual patients to develop a treatment plan with optimal factor dosing. At the very least, many hematologists require a current inhibitor titer to rule out recent inhibitor development that would drastically diminish the effectiveness of factor with surgical treatment.

The surgical treatment plan for people with BDOs typically includes a target peak preoperative factor level, a trough range, and duration for the treatment. Setting the desired peak and trough helps the provider determine which product should be used to achieve the targets, and which delivery method and frequency of administration will be used.[7] Although there is wide variety in protocols used in surgical procedures for those with BDOs, the preoperative target peak level is found to be fairly consistent across several review articles.[7] The most common peak preoperative factor goal in the developed world ranges from 80% to 120%. If a PK profile has not been performed, it can be achieved using the expected recovery for each product. Initial peak factor level goals typically are achieved using bolus intravenous (IV) dosing. Factor should be reconstituted according to package directions and given over the time frames advised by the manufacturer.

Meeting trough goals is important because it is at the lower factor levels that pathologic bleeding may occur. Factor troughs can be managed by repeat bolus dosing or through continuous infusion of factor. Frequency of bolus dosing is product- and patient dependent because of differences in the half-life of each product and variations in individual PK profiles. The advantage of continuous infusion is that a steady-state factor level can be maintained without high peak levels and dangerously low troughs.

Continuous infusion is considered cost-effective because less factor is used when steady factor levels are maintained.[11] A frequent finding in the use of continuous infusion of factor is to have factor levels rise on postoperative day 3 to 5 because of decreased plasma clearance that occurs when the optimum factor level is achieved.[9] The infusion rate is often decreased at this time to maintain the desired factor level.

Factor used in continuous infusions must be prepared under sterile conditions. It should be diluted according to package instructions, with minimal additional diluent added to the product. Because newer factor products use less diluent volume, a parallel normal saline infusion often must be provided to keep a line open. Continuous infusion requires the use of a portable syringe pump or mini-cassette infusion pump and can be administered in the inpatient or ambulatory setting. Once factor has been reconstituted for use in continuous infusion, it has been shown to remain stable for between 24 and 72 hours.[11]

Continuous infusion of factor requires dependable venous access,[9] which is often the most challenging aspect of factor treatment in people with BDOs. Implanted ports, CVADs, and peripherally inserted central catheters are often chosen to provide reliable venous access for continuous infusion in the perioperative period. Meticulous attention to catheter care is vital for infection prevention.

Factor levels are commonly monitored to tailor perioperative therapy. For effective perioperative factor-level monitoring, there must be a local laboratory with the capability of resulting factor levels quickly. Having a turnaround time for factor levels of no more than 2 to 3 hours is essential for management of therapeutic treatment.[12] Some providers who do not have a specialty coagulation laboratory capable of running STAT factor levels use screening tests, such as the prothrombin or the activated partial thromboplastin time tests, to monitor coagulation. However, factor levels can be subtherapeutic with normal screening labs. More current testing methods, such as the thromboelastograph (TEG), may be available in some settings. TEG has the advantage of creating a graph of all stages of coagulation very quickly, allowing for adjustment of therapy, and is especially helpful in monitoring nonhemophilia BDOs, such as afibrinogenemia and platelet dysfunctions.

TABLE 2

Antifibrinolytic Therapy

Medication	Available Forms	Recommended Dosing
Aminocaproic acid (Amicar)	Oral 250 mg/mL liquid 500-mg tabs 1000-mg tabs IV	100 mg/kg Q 6 h; max dose 6000 mg
Tranexamic acid	IV	10 mg/kg Q 8 h
Tranexamic acid (Lysteda)	650-mg tabs	1300 mg PO Q 12 h or 25 mg/kg Q 8 h

Abbreviations: IV, intravenous.

ADJUVANT MEDICATIONS

Adjuvant medications are often used as perioperative treatment for persons with BDOs. Antifibrinolytics slow the breakdown of blood clots in the surgical bed. They are especially effective in mucous membrane bleeding. At least half of European hematology teams report using an antifibrinolytic along with medication to increase factor levels in most surgical procedures at their centers.[7] Current available antifibrinolytics are aminocaproic acid and tranexamic acid. Both are available for IV and oral administration (Table 2). Topical preparations, such as fibrin glue, thrombin preparations, and meticulous suturing, are common additions to the hemostasis armament for treatment of BDO patients.

VON WILLEBRAND DISEASE

Those with mild hemophilia A or vWD type 1 (the mildest form) may respond to treatment with desmopressin acetate (DDAVP) with an increase in their circulating factor VIII and von Willebrand factor levels. This response should be established before use of the medication for surgical treatment by administering a test dose and repeating factor levels to confirm response. DDAVP is a synthetic analogue of the naturally occurring hormone vasopressin. Mechanism of action is thought to be the result of temporary vasoconstriction, which causes the release of factor VIII and von Willebrand factor antigen from endothelial storage sites.[13]

The use of DDAVP for surgical prophylaxis is limited by the fact that tachyphylaxis occurs after 3 to 4 doses. If the surgical treatment plan requires increasing the factor levels for longer than 3 to 5 days, a factor replacement product will have to be used to prevent bleeding. DDAVP can be given intravenously, subcutaneously, or by using the highly concentrated nasal spray form. All forms of DDAVP require the user to follow a moderate fluid restriction for 12 to 24 hours after each dose of the medication to avoid dilutional hyponatremia.

Persons with vWD type 2 or type 3 most often are treated with factor replacement products. Currently available von Willebrand factor-containing products are plasma derived.[8] These products may be labeled with both factor VIII and von Willebrand factor units, so care should be taken to ensure that the ordered dose is used.

INHIBITORS

Inhibitors to infused factor are a challenging complication for persons with BDOs. Inhibitors are alloantibodies that cause factor given to treat bleeding to become inactivated. Inhibitors develop in 20% to 30% of patients with severe hemophilia A and less frequently in 2% to 5% of patients with severe hemophilia B.[14] There are reports of inhibitors to von Willebrand factor complicating treatment of patients with vWD.

Inhibitors are often found in the first 50 treatment days. When found, they make surgical treatment more challenging. Inhibitors to factor are categorized as high titer (more than 5 Bethesda units [BUs]) or low titer (less than 5 BUs). Low-titer inhibitors often can be treated with higher-than-normal doses of factor; high-titer inhibitors require the use of bypassing agents. Currently available bypassing agents include recombinant activated factor VII (rfVIIa) or an activated prothrombin complex concentrate (aPCC). Bypassing agents most often are used by bolus dosing only, although there have been reports in the literature describing continuous infusion with rfVIIa.

Bypassing agents are reported to have variable efficacies and are difficult to monitor. No direct laboratory tests are available to measure therapeutic effect. All adjunctive therapeutic measures available, such as antifibrinolytics, thrombin preparations, and mechanical devices, should be used. For this reason, surgical procedures in patients with hemophilia complicated by a high-titer inhibitor should be undertaken with caution, and elective surgical procedures should be avoided.[14,15]

POSTOPERATIVE CARE

Antihemophilic factor or DDAVP should be repeated as ordered, with a preference for therapeutic dosing to be given in the mornings. This allows for the highest factor levels to be experienced during the most active time of day. Lower factor levels following a morning infusion will occur at night, while the patient is sleeping, and will be less likely to result in pathologic bleeding. Antifibrinolytics should be given around the clock for best therapeutic effect.

Postoperative pain in patients with BDOs should be treated effectively. Many people with BDOs live with chronic pain because of frequent joint and muscle bleeds throughout their lives. Patients are often discouraged from taking nonsteroidal anti-inflammatory (NSAID) medications because of the inhibitory effect of NSAIDs on platelet aggregation, which is thought to worsen bleeding in those with BDOs. Some patients with BDOs have a history of long-standing narcotic use and will have a high tolerance for the medications when they are used for acute postoperative pain. Recovery from surgical procedures will be quicker and more effective if pain is anticipated and treated adequately.[16] Consideration of a pain management consult for help in managing this situation is advised.

RICE (rest, ice, compression, and elevation) is an old standby and is often used postoperatively to treat patients with BDOs. Rest allows damaged tissue to heal and prevents additional tissue injury. Although early mobilization is advised in most postoperative situations, protection of the surgical site can be achieved by encouraging ambulation only and deferring athletic activities or carrying items heavier than 10 pounds for 2 to 3 weeks. Application of cold has long been a mainstay to treat bleeding in persons with BDOs. It was thought to slow blood flow to the affected area, leading to decreased blood loss. However, recent data suggest that low temperature is associated with impairment of coagulation enzyme activity and platelet function.[17] On the basis of this new information, it is recommended that cold not be used alone. When it is used, it should be applied for no more than 15 to 20 minutes, then removed for at least 45 minutes to allow for restored blood flow.

Compression may be provided by elastic wraps or other devices, but should allow adequate circulation and visualization of the surgical wound to ensure that bleeding and edema do not occur unnoticed. Elevation of the affected body part above the level of the heart, if possible, can help limit postoperative edema at the surgical site.

Surgical drains should be monitored closely for output. Volume and characteristics of the drainage should be observed, recorded, and reported to the treatment team. Medication to raise the factor level should be considered for drain removal, which often disturbs healing tissues, producing fresh bleeding.[16]

Postoperative physical therapy (PT) is often ordered for patients with BDOs who have undergone orthopedic surgery. It can be initiated as early as postop day 1 and is used intermittently during hospital admission, as well as after discharge. PT goals will include restoration of joint range of motion and strength. These, along with increasing endurance, will require as much as 6 to 8 weeks of therapy. Clotting factor replacement must be used before PT sessions to prevent postoperative bleeding.[16]

POSTOPERATIVE COMPLICATIONS

Postoperative bleeding is a complication that may occur in people with BDOs. Bleeding may be immediate or delayed, sometimes as long as 5 to 21 days after the surgery,[4] and it may be visible in the form of bruising, hematomas, or frank bleeding from the surgical wound. It may be less obvious, however, in the case of bleeding into a body cavity, organ, joint, or muscle. Bleeding that is not visible may be evidenced by swelling, increased pain at the site, or a sudden drop in hemoglobin or blood pressure. Systemic indications of hemorrhage, such as tachycardia, tachypnea, hypotension, and orthostatic hypotension, should be noted and treated as medical emergencies.[18]

Postoperative bleeding may require the administration of additional factor and blood product. Surgical response to postoperative bleeding may be evacuation of the hematoma or cauterization of the wound bed. Nurses caring for BDO patients in the postoperative period should have a high index of suspicion for the complication of bleeding, and should respond with appropriate urgency in assessment and treatment of the bleeding in communication with the treating physicians. Bleeding should be reported to the hematologist and to the surgeon for a coordinated response to care.

Infection of the surgical wound is a serious complication in the postoperative period. The risk of immediate postoperative infection in patients with BDOs does not appear to be increased over that of the general population. However, people with hemophilia are at greater risk for secondary infection, and the risk increases when prosthetic hardware is used, such as in hip and knee arthroplasty.[16] The increased risk continues throughout the person's life span. It is thought that the source of bacteremia is through contamination via IV factor infusions, so meticulous care should be taken with IV access to avoid this.

THROMBOSIS RISK

Because patients with BDOs are at high risk of bleeding, it has been thought that their risk of venous thromboembolism and pulmonary embolism in the postoperative period was decreased over that of the general population. However, it seems that treatment given to people with BDOs to prevent bleeding may increase the risk of pathologic thrombosis in the postoperative period. The risk of thrombosis is increased with prolonged immobility, which patients may experience after total knee or hip arthroplasty. Other conditions that may increase the risk of postoperative thrombosis include increased age, obesity, the use of aPCCs, factor VIII levels greater than 150%, and the use of antifibrinolytics concomitant with factor replacement.

There is no consensus in the hemophilia community regarding whether thromboprophylaxis with anticoagulants should be used postoperatively in persons with BDOs.[19] However, nearly all hematologists involved in the care of people with BDOs in the postoperative period agree that mechanical methods of prophylaxis, such as sequential compression devices and early ambulation, are useful methods for the prevention of deep vein thrombosis and thromboembolism.

Many hematologists, along with orthopedic surgeons and chest physicians, adhere to the perspective that giving perioperative factor prophylaxis to patients with BDOs creates a nearly normal clotting profile and exposes them to the risk of thromboembolism that approaches that of the general population.[20] Recommendations for the use of low-molecular-weight heparin beginning 6 to 12 hours postoperatively may help decrease the risk of intraoperative bleeding and decrease the risk of thromboembolism.[21] If antithrombotic therapy is used, it should be used with factor replacement for 3 to 4 weeks and monitored closely to avoid unintended bleeding. People with BDOs who have inhibitors are treated with bypassing agents and are at higher risk for postoperative bleeding. They are rarely prescribed antithrombotic therapy. In these cases, early mobilization may be the best option for thrombosis prophylaxis.[14,15]

ISCHEMIC HEART DISEASE

As treatment options and health care availability have increased for people with BDOs, their life expectancy has lengthened and now approaches that of the general population.[20] With longer life expectancy has come increased prevalence of age-related disorders, such as cardiovascular disease. Although it has been thought that people with BDOs have a lower risk of developing cardiac disease, there seems to be increasing evidence that they are at risk for conditions such as ischemic heart disease (IHD) as they age. Factors that increase the potential for the development of IHD include atherosclerosis, hypertension, obesity, and smoking. In addition, people with BDOs who also have HIV infection and take highly active antiretroviral medications (HAART) are at increased risk for the development of cardiovascular disease as a result of the metabolic syndrome that frequently accompanies HAART therapy.[21]

Evidence-based guidelines for the treatment of IHD in people with BDOs are scarce. Invasive procedures such as cardiac catheterization and other percutaneous coronary interventions, along with antithrombotic therapy associated with this treatment, should be managed as any other invasive procedure in the BDO population. Treatment to prevent bleeding and to minimize the risk of thrombosis should be managed with close cooperation between the treating cardiology and hematology teams.[19]

When cardiac reperfusion with stenting is required, bare metal stents are often preferred to the use of drug-eluting stents because this decreases the period of time that antiplatelet therapy will be needed after stenting. Prophylactic factor replacement is often given 2 to 3 times a week during the entire period that antiplatelet therapy is used. In many cases, low-dose aspirin can then be used prophylactically after the acute phase without an increase in bleeding symptoms.[19]

SPECIAL CONSIDERATIONS FOR INFUSION NURSES

Infusion nurses have a vital role in caring for people with BDOs in the perioperative period. Management of the treatment plan that balances hemostasis with thromboprophylaxis requires close attention to detail and ongoing communication with the hematology and surgical teams. Meticulous care of IV access devices to ensure that medications are delivered appropriately and that infections are avoided are critical in the postoperative care of the patient. Attention to wound healing and awareness of the symptoms of possible postoperative bleeding or thrombosis are required, as is assistance with pain management. Finally, education of the patient and family to increase their understanding and commitment to the treatment plan supports the efforts of the primary teams to ensure the best possible outcome for the patient.

REFERENCES

1. Ljung R, Knobe K. How to manage invasive procedures in children with haemophilia. *Br J Haematol.* 2012;157(5):519-528.
2. Pasi K, Collins P, Keeling D, et al. Management of von Willebrand disease: a guideline from the UK haemophilia centre doctors' organization. *Haemophilia.* 2004;10(3):218-231.
3. Watts R, Cook R. Operative management and outcomes in children with congenital bleeding disorders: a retrospective review at a single haemophilia treatment center. *Haemophilia.* 2012;18(3):421-425.
4. Kitchens C. Surgery in hemophilia and related disorders: a prospective study of 100 consecutive procedures. *Medicine.* 1986;65(1):34-45.
5. Rodriguez-Merchan E. Surgical wound healing in bleeding disorders. *Haemophilia.* 2012;18(4):487-490.
6. Hoffman M, Harger A, Lenkowski A, Hedner U, Roberts H, Monroe D. Cutaneous wound healing is impaired in hemophilia B. *Blood.* 2006;108(9):3053-3060.
7. Hermans C, Altisent C, Batorova A, et al. Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey, and recommendations. *Haemophilia.* 2009;15(3):639-658.
8. Kauffman J. Recombinant infusion therapies indicated for bleeding disorders. *J Infus Nurs.* 2011;3(1):29-35.

9. Morfini M. Secondary prophylaxis with factor IX concentrates: continuous infusion. *Blood Transfus*. 2008;6(2S):S21-S25.
10. Shapiro A, Korth-Bradley J, Poon M. Use of pharmacokinetics in the coagulation factor treatment of patients with haemophilia. *Haemophilia*. 2005;1(6):571-582.
11. Batorova A, Martinowitz U. Continuous infusion of coagulation factors: current opinion. *Curr Opin Hematol*. 2006;13(5):308-315.
12. Escobar M, Maahs J, Hellman E, et al. Multidisciplinary management of patients with haemophilia with inhibitors undergoing surgery in the United States: perspectives and best practices derived from experienced treatment centers. *Haemophilia*. 2012;18:971-981.
13. National Heart Lung and Blood Institute. The diagnosis, evaluation and management of von Willebrand disease (VWD). 2006. http://www.nhlbi.nih.gov/guidelines/vwd.
14. Shapiro A, Cooper D. US survey of surgical capabilities and experience with surgical procedures in patients with congenital haemophilia with inhibitors. *Haemophilia*. 2012;18(3):400-405.
15. Kempton C, White G. How we treat a hemophilia A patient with a factor VIII inhibitor. *Blood*. 2009;113(1):11-17.
16. Wiedel J, Stabler S, Geraghty S, Funk S. *Joint Replacement Surgery in Hemophilia*. Montreal, Quebec, Canada: World Federation of Hemophilia; 2010.
17. Forsyth A, Rivard G, Valentino L, et al. Consequences of intra-articular bleeding in haemophilia: science to clinical practice and beyond. *Haemophilia*. 2012;18(S4):112-119.
18. Sahu S, Singh S, Kumar M. Revisiting hemophilia management in acute medicine. *J Emerg Trauma Shock*. 2011;4(2):292-298.
19. Mannucci P, Mauser-Bunschoten E. Cardiovascular disease in haemophilia patients: a contemporary issue. *Haemophilia*. 2010;16(S3):58-66.
20. Stein M, Park J, Raterman S. Prevention of VTE following total hip and knee arthroplasty in hemophilia patients. *Orthopedics*. 2011;34(5):389-392.
21. Mannucci P, Schutgens R, Santagostino E, Mauser-Bunschoten E. How I treat age-related morbidities in elderly persons with hemophilia. *Blood*. 2009;114(26):5256-5263.