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Optimal Management of Elective Joint Replacement Surgery in Patients with Hemophilia

Oana-Viola Badulescu, Iris Bararu Bojan, Maria Vladeanu, Codruta Badescu, Andrei Bojan, Paul Dan Sirbu and Manuela Ciocoiu

Abstract

Hemophilia is a genetic or acquired disease that leads to spontaneous and recurrent bleedings, which affect the joints and muscles, thus determining chronic damage to the cartilage which will lead to joint disease and hemophilic arthropathy. Even though hemophilic patients were initially thought to have a low incidence of atherothrombotic complications, it is now clear that atherothrombotic events occur. The administration of plasmatic factor VIII has better clinical results in type A hemophilic patients than the transfusion with plasma. We analyzed five patients with hemophilia type A, aged between 35 and 62 years. Two of them had a severe form of hemophilia with factor VIII less than 1%, while the other three had a moderate form with factor VIII ranging between 1 and 5%. The five patients underwent total knee repair interventions and received substitution treatment with clotting factors but also prophylactic anticoagulant treatment. The postsurgical evolution of these patients was favorable, with similar hemostatic profile as the non-hemophilic patients. Moroctocog alfa is an efficient substitutive treatment that manages to normalize the hemostatic profile of patients. Therefore, it is recommended to provide prophylactic antithrombotic therapy after the orthopedic interventions.

Keywords: hemophilia, hemophilic arthropathy, orthopedic surgery, hemostasis, physiotherapy

1. Introduction

Hemophilia is a disease that has a frequency of approximately 1 in 10,000 births. It has an X-linked transmission, and it consists in a bleeding disorder due to the deficiency of clotting factor VIII (hemophilia A) or factor IX (hemophilia B). Hemophilia is a genetic or acquired disease that leads to spontaneous and recurrent bleedings, which affect the joints and muscles, thus determining chronic damage to the cartilage which will lead to joint disease and hemophilic arthropathy.

There are two major types of hemophilia: type A and type B. These disorders are X-linked and consist in hemorrhages, resulting from diminished levels of clotting factors VIII and IX. Type A is 5–6 times more frequent than type B. This pathology

affects in a symptomatic manner only male patients and is characterized by excessive bleeding, which is installed rather spontaneously or after minimal incidents, and is difficult to stop [1].

Hemophilia is a chronic condition that requires a substitution treatment with the defective factor. Its severity varies accordingly to the residual factor level. It is classified as severe (when the clotting factor activity is less than 1%), moderate (1–5%), and mild (6–40%).

If not treated hemophilic patients, especially those with very low clotting factor activity and severe disease, have recurrent disabling and life-threatening bleeding episodes. Using prophylactic factor therapy may diminish bleeding; therefore these novel therapies have changed the prognosis of hemophilic patients, providing increased life expectancy and better quality of life [2–4].

Even though hemophilic patients were initially thought to have a low incidence of atherothrombotic complications, it is now clear that atherothrombotic events occur.

Limited data suggest that hemophilia is not protective against atherosclerosis and thrombosis, but this theory is still to be studied in men with severe forms of hemophilia without other CVD risk factors, such as active HIV infection [5].

The most common manifestation of hemophilia is represented by bleeding. The severity of hemorrhages is correlated with the plasmatic level of clotting factors. Therefore, there are patients with mild or minor hemophilia that may not bleed excessively until they undergo a surgical intervention or after a trauma.

The accurate diagnostic of hemophilia is mandatory for an optimal management. Hemophilia should be suspected in patients with early bruising in childhood, with excessive hemorrhages after trauma or surgical intervention, or in patients with spontaneous bleeding.

2. Principles of care

Patients with hemophilia need a complex therapeutical management. The most important aim is to administrate the deficient clotting factor so that bleedings are terminated or prevented. If an acute bleeding occurs, it is important to treat it in the first 2 hours.

In order to ease the appropriate management, all patients should carry upon them accessible identification information such as diagnosis, severity of bleeding disorder, type of treatment product that should be used, and contact information.

The patients with hemophilia should benefit from a comprehensive care treatment provided by a team of specialists. This type of care should increase the quality of life while reducing morbidity and mortality.

Hemophilic patients should benefit from fitness and physical activity therapy, in order to obtain normal neuromuscular development, coordination, healthy body weight, and appropriate self-esteem [6].

Adjunctive therapy should be provided consisting in physiotherapy, antifibrinolytic drugs, and certain COX-2 inhibitors in order to soothe the pain.

Prophylactic factor replacement therapy should be administrated so that bleeding and joint destruction is prevented, thus preserving a normal musculoskeletal function.

Surgery is required for complications related to hemophilia or for unrelated disease. The surgical treatment should be done in a comprehensive treatment center for hemophilia [7, 8].

3. Complications of hemophilia

In the majority of cases (90%), the bleeding episodes in hemophilic patients occur in the joints, thus leading to hemarthrosis. From all these bleedings, the most affected joints are the knees, elbows, and ankles. The affected articulation is usually swollen, held in flexion, the mobility being very restricted and painful.

If the deficient clotting factor is given quickly, the hemorrhages can be controlled, and the episode can benefit from conservative orthopedic treatment without long-term complications.

If the bleeding persists or if hemorrhages reoccur, the presence of blood in the joint may lead to apoptosis of the chondrocytes. When there is too much blood present, the synovial membrane will become hypertrophic as it tries to reabsorb the blood. From that moment a vicious circle of chronic synovitis develops thus leading to joint destruction and to hemophilic arthropathy [9, 10] (**Figure 1**).

The hypertrophic synovial membrane consists of villous formation with increased vascularization and chronic inflammatory process. Hemophilic children will have hypertrophic epiphyseal growth plates. This bone hypertrophy can determine length discrepancies and modifications in contour and angular deformities. Further destruction of the cartilage may appear if the inflammatory and hemorrhagic process is not controlled. When the synoviocytes are destroyed, they release lysosomal enzymes that promote further cartilage destruction and promote chronic inflammation. As the modifications progressively occur and the cartilage of the joint degrades, the joint function diminishes, and there are limited and painful movements [12–14].

The apparition of hemarthrosis is the most frequent and unfavorable clinical expression of a hemorrhage in a hemophilic patient; it has an incidence of 75%. It usually appears between 1 and 5 years; if it does occur after 10 years, it is usually due to a mitigated condition. The other symptoms that may appear are relapses. The trigger is represented by a trauma which is very frequently unnoticeable. The most affected joints are in a decreasing order as follows: knees (36%), ankle (30%), elbow (23%), hand (6%), shoulder (3%), and hip (2%) [15, 16].

Hemarthrosis usually affects only one joint, but sometimes the bleeding may be present in both joints, but the lesions are not symmetric. Relapses usually affect the same articulation. Each bleeding episode determines disorders of the joint, thus creating a predisposition for a relapse. The joint structures will weaken, the muscles become atrophic and develop fibrosis thus the joint functionality becomes mechanics deficient. In order to bleed less, the synovial will become hypertrophic and will have an increased vascularization, and this mechanism will lead to a vicious circle. From this moment on, a chronic condition begins and is called “hemophilic arthropathy.” This complication advances slowly during time and induces severe modification of the joint with ankylosis. Some experimental studies have proven that a major hemarthrosis induces



Figure 1.
Modifications of hemarthrosis in hemophilia [11].

in the cavity of the joint a dense inflammatory process, while the local tissues change their color and become brownish as a result of the hemosiderin deposits that are due to the erythrocyte damage. The vessels become hyperplastic, thus creating brittle vessels, which are prone to bleeding, therefore inducing a vicious circle: bleeding-vascular hyperplasia-bleeding [11, 17, 18].

The surface of the articulation roughens and pannus is formed. The bone located in the subchondral region becomes dysmorphic. After 30 days the erosions present in the cartilage and bone are obvious.

Different studies have proven that the affected joints are an important factor in inducing cartilage destruction in hemophilic patients. Different authors showed that the presence of iron in the intra-articular blood induces molecular modifications that can offer an explanation for the cellular proliferation in the synovial membrane (synovitis).

Valentino et al. proved in an experimental study that the bleeding that results from a controlled trauma causes joint swelling, synovitis, and hemophilic arthropathy.

In order to alleviate these complications, substitutive treatment with deficient coagulation factor applied from a young age (primary prophylaxis) represents the best therapeutic conduct. Even though primary prophylaxis with the deficient clotting factor is given despite, some patients still have intra-articular hemorrhages, as a result of an insufficient dose of coagulation factor or due to a diminished adherence to the therapy, while other hemophilic patients may present sub-clinically manifested hemarthroses [19, 20].

If continuous prophylactic therapy with clotting factors is provided, the natural course of the arthropathy can be slowed down. One of the most threatening complications of the therapy with clotting factors is the apparition of alloantibodies that are directed against the exogenous molecules of clotting factor. This complication appears in one third of the patients, and it increases the likelihood to develop an uncontrolled bleeding [20, 21].

4. Emicizumab

There has been a new drug developed for the treatment of hemophilic patients. It is called emicizumab, and it is a recombinant antibody that brings activated factor IXa and factor X into an adequate conformation that will lead to the activation of factor X and therefore will mimic the cofactor function of factor VIIIa. A subcutaneous injection with emicizumab that is given once weekly proves to be an efficient method to prevent bleeding in the majority of type A hemophilic patients with inhibitors to factor VIII. Even more the prevention of bleeding has been observed in 66% of patients without inhibitors to factor VIII.

5. Moroctocog alfa

The administration of plasmatic factor VIII has better clinical results in type A hemophilic patients than the transfusion with plasma. The side effects are linked to viral infections transmission such as hepatitis B, C, or HIV; therefore it is better to use in clinical practice recombinant clotting factors that are associated with a diminished risk of viral transmission. In order to have safer products, there have been more modern generations of recombinant factor VIII (rFVIII) developed, the viral transmission being much lower with each new generation of compounds. The first generation had a human serum albumin in order to stabilize the

product. The second-generation compounds have no albumin in their composition, but proteins from humans or animals were still allowed in the process of cell culture. The third-generation compounds have eliminated animal and human proteins, but contain murine monoclonal antibodies, which are still used for the purification of rFVIII. It was proven that the elimination of the middle portion (domain B) of the wild-type FVIII did not diminish the clotting activity. It was also shown that the full-length protein had similar effects. These findings helped to discover the recombinant FVIII with deletion of the B domain called moroctocog alfa [21, 22].

ReFacto® is a recombinant clotting factor VIII which has a B-domain deletion (moroctocog alfa). It has a molecular weight of about 170,000 Da and contains 1438 amino acids.

ReFacto has a similar functionality as endogenous clotting factor VIII. When given to a patient with hemophilia, factor VIII will bind to the patient's intrinsic von Willebrand factor. When activated factor VIII becomes a cofactor for activated factor IX, thus catalyzing the activation of factor X. The activated factor X will subsequently transform prothrombin in thrombin. The latter will transform fibrinogen in fibrin, thus forming the red clot. When giving substitution treatment, the levels of factor VIII increase, and the deficiency is temporarily corrected, thus leading to a diminishment in bleeding episodes [1, 23].

6. Personal clinical experience

We analyzed five patients with hemophilia type A, aged between 35 and 62 years. Two of them had a severe form of hemophilia with factor VIII less than 1%, while the other three had a moderate form with factor VIII ranging between 1 and 5%. All of them described intense pain as a result of functionally chronic knee arthropathies. Thus, the lesions had an indication of endoprosthesis and total knee repair. These orthopedic interventions were done by a multidisciplinary team, formed by hematologists, orthopedists, and intensive care staff (**Figure 2**).

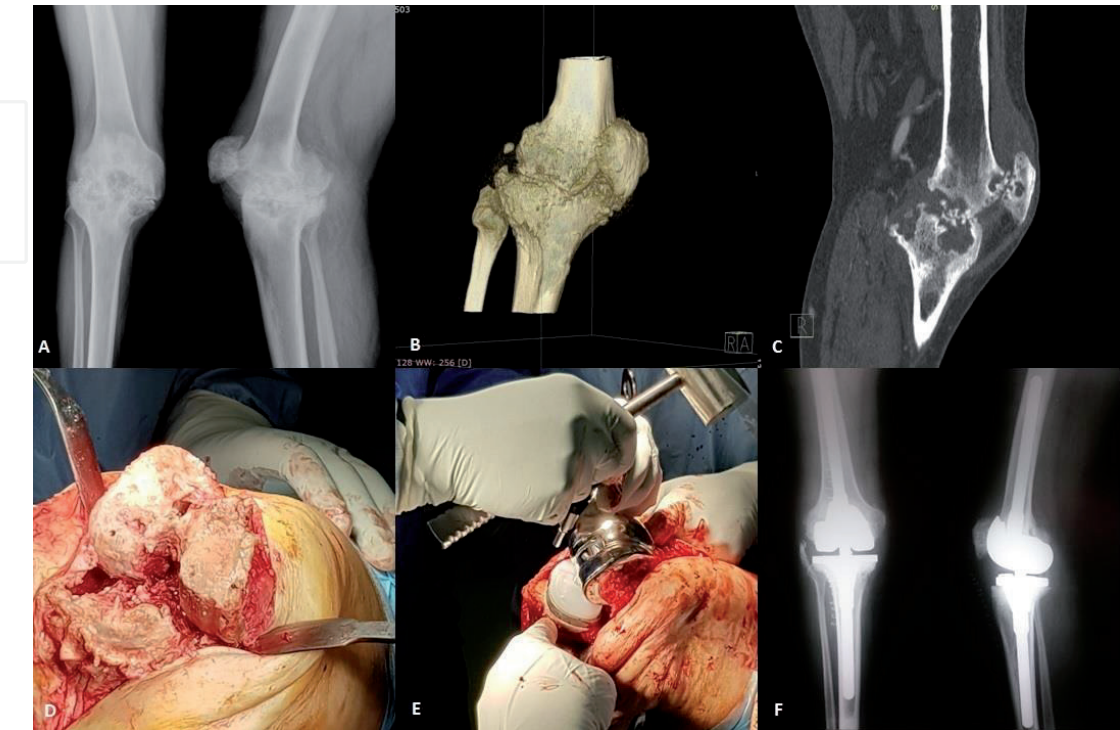


Figure 2.
TKR for severe hemophilic osteoarthritis.

The orthopedic surgeries were realized after a rigorous hematological control, offered through the national protocol for hemophilia. Therefore, all patients received the necessary amount of substitution therapy with clotting factor. During the surgery and in the postprocedural surveillance period, the patients had their blood count, hemostasis, and transfusion requirements very thoroughly assessed. Also, other postsurgical complications were routinely searched (**Figure 3**).

The postsurgical evolution of these patients was favorable, with similar hemostatic profile as the non-hemophilic patients. Only one patient had increased bleeding times, as his clotting profile associated also a factor VII deficiency, thus requiring blood transfusion.

After the administration of Moroctocog alpha substitution treatment, all five patients had a normal clotting profile, thus requiring thromboprophylaxis with LMVH (enoxaparin) in order to prevent VTE. An important aspect to be noted refers to the fact that the amount of bleeding did not correlate with the levels of residual factor. Even more, we noted no differences regarding the volume of blood drained after the surgery between patients with moderate or severe hemophilia. The elderly patients had similar outcomes with young patients with favorable postoperative prognosis, consisting in diminishment of joint pain, improvement in



Figure 3. Severe axial deformity. Genu varum in severe hemophilic arthropathy. (A–B) Preoperative X-rays. (C–D) Severe genu varum clinically and radiologically. (E–F) Postoperative X-rays. (G–H) Clinical view of the knee with axis restored and wound healed.

functionality, and increased quality of life. We thus concluded that older age is not a contraindication for complex surgical intervention.

The systemic substitutive treatment was very efficient and normalized the clotting profile of the patients. Therefore, the surgical hemostasis was done without using topical agents such as bio surgical gels or foams. Even more the intrasurgical bleeding of these patients was similar with the hemorrhage seen in patients without the diagnosis of hemophilia. The monitorization of the clotting profile of the patients was thoroughly done by a hematologist trained in treating hemophilic patients requiring elective surgeries. The administration of the substitution therapy followed the guidelines described in the National Protocol of Hemophilia. The clotting profile was monitored daily, and the results showed a normal hemostasis after the administration of treatment. That is why we decided to give low-molecular-weight heparin in these patients, as the risk of thromboembolic events increased after the normalization of the hemostasis, due to the associated risk factors (age, sedentarism, obesity, cardiovascular disease). We chose to give enoxaparin once daily in a 1 mg/kg dose, and the clinical and paraclinical results were favorable.

7. Prophylaxy of thrombosis in hemophilic patients who undergo orthopedic surgeries

Pruthi et al. published a paper in 2000 regarding the use of thrombophylaxy in patients with hemophilia. They presented the case of a patient with moderate hemophilia B, who underwent treatment with factor IX concentrate in order to realize a total hip replacement for a hip fracture and developed venous thromboembolism in the operated limb after the intervention. The thrombophilia screening detected the presence of a heterozygous type of factor V Leiden mutation [24]. Therefore, the authors concluded that presurgical screening for thrombophilia is useful in hemophilic patients who had a previous history of VTE. Another research realized by Mannucci the same year suggested that all patients with thrombophilia should receive short-term therapy with LMWH if they are exposed to significant risks such as prolonged immobilization or surgery [25].

Later in 2004, Dargaud et al. suggested that hemophilic patients should not routinely receive thromboprophylaxis as there are not enough studies, but they also added that hemophilia per se does not protect against venous thromboembolism. The conclusion of this study was that specific cases with increased risk of thrombosis should receive therapy with LMWH [26]. In 2006 Butcher and Pasi reported the case of a patient with hemophilia A, who developed an episode of massive pulmonary embolism after major pelvic surgery. Thus, they concluded that thromboprophylaxis in selected hemophilic patients is very important [27].

Another research done by Uprichard et al. in 2012 included 13 patients with total kidney replacement, from which 11 had hemophilia B. They received mechanical thromboprophylaxis, and one also received pharmacological treatment. The results were satisfying as no patient suffered VTE [28].

In 2012, Uprichard et al. analyzed a series of 13 TKRs in 11 patients with hemophilia B, who received mechanical thromboprophylaxis, and 1 also received pharmacological thromboprophylaxis. No patients suffered VTE [29].

On the other hand, another study realized by Krekeler et al. in 2012 analyzed 105 interventions, 90 of them being major orthopedic surgeries and 15 minor surgeries. The authors did not find any case of VTE even though therapy with LWMH wasn't given after the surgery. In the same year Ozelo arrived as the same conclusion as Butcher and Pasi. Another research from 2013 done by Berntorp stated that in case of elderly patients diagnosed with hemophilia or patients with von Willebrand

disease, a rigorous assessment of the risk and benefit of thromboprophylaxis in the patients who underwent major orthopedic surgery should be realized.

Ozelo et al. proved that the use of graduated compression stockings and early mobilization is sufficient in preventing VTE in the majority of patients. Thus, the administration of ant clotting therapies should be taken into account just for patients that have strong additional risk factors for thrombosis. Contrary, patients with hemophilia treated with inhibitors should not receive pharmacological thromboprophylaxis. Patients with von Willebrand disease, who receive replacement therapy with factor concentrates and who underwent surgical procedures, should have a strict monitorization of FVIII plasma levels, and thromboprophylaxis should be taken into account if there are other thrombotic risk factors [30–32].

8. Conclusions

The best therapy for hemophilic patients consists in doing primary prophylaxis so joint bleeding and other complications are prevented. Even though orthopedic surgeries in these patients are associated with increased risk of complications such as infections and hemorrhages, they can increase significantly the joint mobility and life quality if they are realized in specialized centers with hematological support. Moroctocog alfa is an efficient substitutive treatment that manages to normalize the hemostatic profile of patients. Therefore, it is recommended to provide prophylactic antithrombotic therapy after the orthopedic interventions.

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References

- [1] Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;**94**(4):566-575. DOI: 10.3324/haematol.2008.001743
- [2] Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia a in the United Kingdom: A 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;**109**:1870-1877
- [3] Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to factor VIII. *Thrombosis and Haemostasis*. 1981;**45**:200-203
- [4] Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia a: A concise review. *American Journal of Hematology*. 2005;**80**:55-63
- [5] Sood SL, Cheng D, Ragni M, et al. A cross-sectional analysis of cardiovascular disease in the hemophilia population. *Blood Advances*. 2018;**2**(11):1325-1333. DOI: 10.1182/bloodadvances.2018018226
- [6] Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Treatment Guidelines Working Group on Behalf of the World Federation of Hemophilia. Guidelines for the Management of Hemophilia. 2nd ed. *Haemophilia*. Jan 2013;**19**(1):e1-e47
- [7] Jansen NW, Roosendaal G, Bijlsmal JW, Degroot J, Lafeber FP. Exposure of human cartilage tissue to low concentrations of blood for a short period of time leads to prolonged cartilage damage: An in vitro study. *Arthritis and Rheumatism*. 2007;**56**:199-207. DOI: 10.1002/art.22304
- [8] Valentino LA, Hakobyan N. Histological changes in murine haemophilic synovitis: A quantitative grading system to assess blood-induced synovitis. *Haemophilia*. 2006;**12**:654-662. DOI: 10.1111/j.1365-2516.2006.01348.x
- [9] Valentino LA, Hakobyan N, Rodriguez N, Hoots WK. Pathogenesis of haemophilic synovitis: Experimental studies on blood-induced joint damage. *Haemophilia*. 2007;**13**(Suppl 3):10-13. DOI: 10.1111/j.1365-2516.2007.01534.x
- [10] Bardas CA, Gabri JZ, Apostu D, Oltean-Dan D, Tomoaia G, Benea H. Functional results of different repair techniques for knee articular cartilage lesions. *Revista de Chimie*. 2018;**69**(11):3288-3291
- [11] Lafeber FP, Miossec P, Valentino LA. Physiopathology of haemophilic arthropathy. *Haemophilia*. 2008;**14**(Suppl 4):3-9. DOI: 10.1111/j.1365-2516.2008.01732.x
- [12] Berea G, Balan G, Sandru V, Sîrbu PD. In vitro three dimensional scaffold-free construct of human adiposederived stem cells in coculture with endothelial cells and fibroblasts. *Revista de Chimie*. 2017;**68**(6):1341-1344
- [13] Hooiveld MJ, Roosendaal G, Jacobs KM, Vianen ME, Van Den Berg HM, Bijlsma JW, et al. Initiation of degenerative joint damage by experimental bleeding combined with loading of the joint: A possible mechanism of hemophilic arthropathy. *Arthritis and Rheumatism*. 2004;**50**:2024-2031. DOI: 10.1002/art.20284
- [14] Hakobyan N, Kazarian T, Jabbar AA, Jabbar KJ, Valentino LA. Pathobiology of hemophilic synovitis I: Overexpression of mdm2 oncogene.

Blood. 2004;**104**:2060-2064. DOI: 10.1182/blood-2003-12-4231

[15] Sirbu PD, Petreus T, Munteanu FL, Perteu M, Lunca S, Poroch V, et al. Clinical experience with a macroporous synthetic bone substitute (eurocer) in the treatment of the patients with bone defects international conference on advancements of medicine and health care through technology. IFMBE Proceedings. 2011;**36**(5):358-368. DOI: 10.1007/978-3-642-22586-4_75

[16] Valentino LA, Hakobyan N, Kazarian T, Jabbar KJ, Jabbar AA. Experimental haemophilic synovitis: Rationale and development of a murine model of human factor VIII deficiency. Haemophilia. 2004;**10**:280-287. DOI: 10.1111/j.1365-2516.2004.00899.x

[17] Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. Journal of Internal Medicine. 1992;**232**:25-32. DOI: 10.1111/j.1365-2796.1992.tb00546.x

[18] Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. The New England Journal of Medicine. 2007;**357**:535-544. DOI: 10.1056/NEJMoa067659

[19] Hilgartner MW. Current treatment of hemophilic arthropathy. Current Opinion in Pediatrics. 2002;**14**:46-49. DOI: 10.1097/00008480-200202000-00008

[20] Rodriguez-Merchan EC. Aspects of current management: Orthopaedic surgery in haemophilia. Haemophilia. 2012;**18**:8-16. DOI: 10.1111/j.1365-2516.2011.02544.x

[21] Korth-Bradley J, Rupon J, Plotka A, Charnigo R, Rendo P. Assessment of

relative bioavailability of moroctocog alfa and moroctocog alfa (AF-CC) in subjects with severe hemophilia A. Clinical and Translational Science. 2018;**11**(3): 283-288. DOI: 10.1111/cts.12544

[22] Kelley B, Jankowski M, Booth J. An improved manufacturing process for Xyntha/ReFacto AF. Haemophilia. 2010;**16**:717-725

[23] Recht M et al. Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor FVIII (BDDrFVIII) for the treatment of haemophilia A: Demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII. Haemophilia. 2009;**15**:869-880

[24] Pruthi RK, Heit JA, Green MM, Emiliusen LM, Nichols WL, Wilke JL, et al. Venous thromboembolism after hip fracture surgery in a patient with haemophilia B and factor V Arg506Gln (factor V Leiden). Haemophilia. 2000;**6**(6):631-634

[25] Santagostino E, Mannucci PM, Bianchi Bonomi A. Guidelines on replacement therapy for haemophilia and inherited coagulation disorders in Italy. Haemophilia. 2000;**6**(1):1-10

[26] Dargaud Y, Meunier S, Negrier C. Haemophilia and thrombophilia: An unexpected association. Haemophilia. 2004;**10**(4):319-326

[27] Butcher JH, Pasi KJ. Fatal postoperative pulmonary embolism in mild haemophilia. Haemophilia. 2006;**12**(2):179-182

[28] Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010. Haemophilia. Jan 2012;**18**(1):46-49

[29] Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: A single-Centre experience, 2000-2010. *Haemophilia*. 2012;**18**(1):46-49

[30] Krekeler S, Alesci S, Miesbach W. Incidence of thromboembolic events after major operations in patients with haemophilia. *Hämostaseologie*. 2012;**32**(Suppl 1):S45-S47

[31] Ozelo MC. Surgery in patients with hemophilia: Is thromboprophylaxis mandatory? *Thrombosis Research*. 2012;**130**(Suppl 1):S23-S26. DOI: 10.1016/j.thromres.2012.08.265.

[32] Lentz SR, Misgav M, Ozelo M, Salek SZ, Veljkovic D, Recht M, et al. Results from a large multinational clinical trial (guardianTM1) using prophylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia a: Safety and efficacy. *Haemophilia*. 2013;**19**(5):691-697