We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

5,500
Open access books available

136,000
International authors and editors

170M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Perioperative Management of Hemophilia A Using Recombinant Factor VIII in Patients Undergoing Major or Minor Surgery

Atsushi Okamoto, Kenta Yamamoto, Go Eguchi,

Yoshitaka Kanai, Terufumi Yamaguchi and Yasuhiro Maeda

Abstract

Among the surgical treatments performed in patients with hemophilia, joint surgery for intra-articular bleeding is the most time-consuming. Previous reports describe the perioperative management of hemophiliacs undergoing coronary artery bypass grafting or of those undergoing cystectomy for treatment of hematuria. In the former study, the patient was elderly; in the latter study, the authors concluded that cystectomy in hemophiliacs is safe if monitored appropriately and that urinary diversion using the intestine should be avoided because anastomotic hemorrhaging may occur. In this study, we discuss coagulation factor replacement therapy for patient with hemophilia A undergoing major or minor surgery.

Keywords: hemophilia, hemophilia with inhibitors, perioperative management, joint surgery

1. Introduction

Due to advancements in coagulation factor preparations, hemophilia treatment has progressed from conventional bleeding replacement therapy to periodic replacement therapy. Historically, the aim has been to perform symptomatic treatment, but currently, the aim of treatment is preventive. Due to bleeding incidents that are characteristic of hemophilia, control of bleeding is particularly important for perioperative patient management. The indication for surgical treatment in patients with hemophilia includes diseases caused by bleeding related to hemophilia as well as those not related to hemophilia. The number of surgeries involving patients with hemophilia is increasing annually.

Due to the development of hemostatic hemostasis treatments, obstacles due to bleeding in young patients are decreasing. However, surgical cases are increasing due to the trend in applying surgery to disorders, which have conventionally been treated nonsurgically and due to an increase in the number of aging patients as a result of improved life expectancy. Due to the reasons stated above, we consider that it is important to stay informed about the latest developments in the perioperative management of patients with hemophilia.

2. Preoperative preparation

Preoperative preparation for hemophiliac patients involves a thorough review of various aspects of the patient's condition. The first parameter to be ascertained is whether the hemophilia is of type A or type B. Following this, the severity of hemophilia needs to be confirmed. Hemophilia is classified based on the blood level of coagulation factors such as factor VIII or factor IX; the disease is characterized as severe when the blood coagulation factor level is less than 1%, moderate if it is 1–5%, and mild if the level is 5% or more. Severity of daily symptoms is generally accepted to reflect the severity of the disease. In patients receiving prophylactic replacement therapy, it is usually necessary to confirm details such as how many units are being administered and how the preparation is being self-injected. The presence of inhibitors (alloantibodies) in the blood needs to be checked as part of the preoperative preparation as well. Although it is known that patients with severe hemophilia are more likely to have developed inhibitors, genetic mutations are known to cause inhibitor formation even in cases with mild disease. Among patients who have received prior treatment, it is also important to check for HCV or HIV infections. Furthermore, if a chronic HCV infection is incident, liver cirrhosis or liver cancer may occur concomitantly, and it is thus necessary to screen patients for these conditions. The abovementioned points may be used as a checklist to evaluate the suitability of patients for surgical procedures. If the abovementioned evaluations reveal no issues, surgery may be performed as per usual protocol. Depending on the magnitude of the surgical invasion, a treatment plan may then be set up, detailing the target levels and of coagulation factors to be maintained, and the duration for which the levels need to be maintained. Regarding treatment planning, it is necessary to administer a necessary and sufficient amount of a coagulation factor preparation to prevent hemorrhagic complications. However, it should also be noted that an overdose of coagulation factor preparations can lead to a risk of thrombosis. The clearance of the coagulation factor preparation varies greatly among patients. In view of this fact, a pharmacokinetic test of factor VIII factor/factor IX preparations ideally to be used for surgery may be conducted preoperatively. Accurate pharmacokinetic profiles may be obtained by measuring coagulation factor activity before administration of the preparation, and 15 minutes, 1, 2, 4, 8, 12, and 24 hours after administration; such an evaluation allows for a proper understanding of the recovery rate and the half-life of the administered factors [1].

3. Selection of coagulation factor replenishment method

There are two main methods of administration of coagulation factor replacement therapy during surgery. The first method is a bolus administration method (BI method), which involves repeated administration of a bolus injections. The second is the continuous administration method (CI method) in which a syringe pump continuously administers coagulation factors after an initial bolus administration. Historically, the stability of the formulations used for coagulation factors has been poor; such formulations needed to be administered as soon as they were thawed. Therefore, perioperative management was predominantly performed using the BI method. In the BI method, when the coagulation factor is injected, the coagulation factor level in the blood exceeds 100% and gradually falls thereafter; when the level approaches 50%, the next bolus is administered. Bolus administration is repeated each time the blood coagulation factor level approaches 50%. The BI method has the advantage of being simple, although the associated disadvantage is that fluctuation in the coagulation

factor levels is high. Intraoperative and postoperative bleeding in recurrent invasive surgery and reoperation is also a serious issue. Recently, however, the stability of the drug and the reliability of the syringe pump have been improved significantly, and the CI method is currently the recommended method for use during major surgery. Using the CI method, the blood clotting ability of hemophilia patients without inhibitors may be restored to that of non-hemophiliac subjects, so that the indication for surgery can be adjusted to the same level as that for non-hemophiliac subjects. Scientific evidence for the effectiveness of the CI method has been accumulating, and there are many reports of surgical cases in which the CI method has been used. However, because the CI method requires specialized expertise, it is desirable to conduct this procedure under the guidance of a hemophilia specialist. The BI and the CI methods have distinct advantages and disadvantages. For routine surgical operations predicted to have less bleeding volume, selection of the BI method according to the situation of the clinical site is appropriate. There have been few systematic studies of the BI method, and hence it cannot be officially recommended. However, as mentioned above, this method has historically been used extensively for numerous types of surgical procedures. The most important advantage of the BI method is that it is a simple method. Application of this method in emergency situations should be decided based on the trough value of the coagulation factor concentration in the blood or when there is insufficient preparation time and insufficient experience with the CI method. If the staff is experienced in performing the CI method, this method may be applied in emergency situations; a provisional administration speed may be used while assuming a coagulation factor concentration of 100%. However, since the optimal administration rate varies greatly among individuals, it is better to monitor the activated partial thromboplastin time (APTT) and the coagulation factor concentration at an early stage. It is also important to check the status of syringe pumps and tubes regularly. Regardless of which method is chosen, when there is a large amount of bleeding, it is necessary not only to supplement the deficient factor but also to replenish other coagulation factors as well as healthy subjects. It is important to understand the advantages and disadvantages of the BI and the CI methods, so as to adopt the method suitable for the individual clinical site and as per the reference guidelines.

4. Important considerations for the use of the continuous administration (CI) method

Even if the target coagulation factor level is set and perioperative management with CI method is executed as planned, the coagulation factor level may not rise as expected. The reason for this may be that the coagulation factor adheres to the surface of the drip tube wall and the assumed dose is not administered. Since the formulations currently used do not include proteins such as albumin, there is a possibility that coagulation factors are lost due to being adsorbed on the tube wall surface when diluted. Therefore, in the case of the CI method, it is necessary to perform injections from the side tube as close to the patient side of the line as possible. During implementation of the CI method, the coagulation factor formulation is placed at room temperature for several hours; this implies that this protein preparation is placed in a harsh environment for an extended period, which makes it difficult to determine the dilution of the preparation and the exact amount that the patient receives. Since the amount of coagulation factor contained in one vial is large, if the preparation is intended to be administered continuously at the determined concentration, the flow rate is usually adjusted to be low, which may result in clogging of the tubes. In order to solve this problem, the use of a low-concentration

formulation such as that of 250 or 500 units is advised. We conclude that the CI method can be performed relatively safely by carefully selecting the appropriate formulation.

5. Intraoperative and postoperative management

Measurement of APTT and factor VIII activity is the most common measurement performed during surgery and postoperative procedures. However, in many institutions, there is delay in obtaining the results of the factor VIII activity tests after sample submission, and thus, APTT is considered to be the most useful way to monitor patient condition, especially during surgery. APTT is helpful if there is not much bleeding. However, if the coagulation factor activity other than that of factor VIII decreases, such as when significant bleeding occurs, APTT may not be normalized even if factor VIII is adequately administered. Changes in APTT are thus difficult to interpret, since APTT is affected by the magnitude of the bleeding volume and also by the degree of liver cirrhosis. However, whether the APTT is within the control level can be evaluated, unless it is extremely extended. In cases where it is not possible to obtain hemostasis either intraoperatively or after surgery despite administration of factors VIII and IX, hemophilia may be assumed as the cause, and treatment for this condition may be instituted. If coagulation factor activities other than those of factor VIII and factor IX are low as in splenectomy for cirrhosis of the liver or when the amount of bleeding is large, levels of other coagulation factors may also decrease. Therefore, when and how much fresh frozen plasma (FFP) is administered should be considered separately.

6. Joint surgery

Due to recent advancements in coagulation factor replacement therapy, it is now possible to prevent intra-articular bleeding right from infancy in children with hemophilia. It is thus possible to prevent escalation of hemophilic arthropathy in such children. On the other hand, if hemophilic synovitis has already occurred and several joints show intra-articular bleeding, arthropathy cannot be prevented, and its progress becomes an issue of concern. In joints with advanced arthropathy, degeneration cannot be avoided, even if subsequent bleeding can be completely prevented. Such degeneration of joints is a major cause of physical dysfunction in adult hemophilia patients. Hemophilic arthropathy is commonly seen in the joints of the elbows, knees, and ankles; in particular, dysfunction of lower limb joints greatly affects daily life. Orthopedic treatments for hemophilic arthropathy include measures against intra-articular bleeding, synovitis, and arthropathy. Specific orthopedic treatments are performed for treating synovitis, such as joint puncture, washing, bleeding, synovial membrane resection for the blood remaining in joints, synovial membrane resection and arthrosis, and artificial joint replacement or arthrodesis. Joint puncture and washing are useful treatment methods and are possible outpatient procedures. In the following sections, we discuss synovectomy, artificial joints, and joint fixation in more detail.

7. Synovectomy

Joints that show recurrent intra-articular bleeding on diagnostic images but do not show arthropathy are the best indications for synovial resection. There are two

major methods of synovectomy, namely, arthroscopic synovectomy (AS) and open synovectomy. Synovial restoration is a method of restoring the synovial membrane by injecting chemical substances (mainly corticosteroids and antibiotics) and radioactive isotopes into joints. Chemical synoviothesis uses chemical substances and results in severe joint pain after the injection; additionally, it is ineffective despite multiple injections to the joints. However, because it is inexpensive, it is frequently performed in developing countries. Radioactive isotope synovectomy (radioactive synoviothesis) is a treatment that can be expected to be effective with a single intra-articular injection, and it is internationally positioned as the first-line therapy for treatment of hemophilic arthritis. In this therapy modality, only beta rays with a shallow arrival depth are generated, and nuclides with a very short half-life are used. The effect of radioactive synoviothesis on genetic material and the articular cartilage have been reported by several publications, and its safety has been reviewed. However, two cases of leukemia have occurred after synovectomy using P^{32}-labeled radionuclides [2], and in 2010, the Medical and Scientific Advisory Council (MASDAC) issued a cautionary note against the application of radioactive isotopes for synovial treatment [3]. Since arthroscopic synovectomy requires hospitalization and the use of adequate coagulation factor preparations, it is generally applied in cases where at least three cycles of radioactive synoviothesis have been ineffective. However, in Japan, arthroscopic synovectomy is the first choice of treatment. An advantage of this method is that other treatments can be added to the treatment regimen; in addition, this method also allows for the observation of the joint surface. It is recommended that arthroscopic synovectomy be performed even in early arthropathy. Invasive synovectomy is a surgical procedure which involves opening the joint capsule and observing the joint under direct vision, so that a wide expanse of the synovium can be removed in a short time. However, the degree of bleeding also increases, and administration of coagulation factor preparations may be necessary to enable installation of artificial joints. In addition, there is also a high risk of contracture after surgery, and thus, this procedure is not frequently performed.

8. Purpose and significance of synovectomy

Intra-articular bleeding caused by severe hemophilia leads to severe swelling of the joints, and the mobility of the affected limb is limited due to pain. When bleeding events happen repeatedly, the synovial membrane proliferates. Treating hematomas and hemosiderin that occur in joints provides relief, but the blood vessels may re-appear on the synovial membrane; the synovial membrane assumes a villous shape and bleeds easily in such conditions. A vicious circle may be established in which synovial proliferation worsens as bleeding events occur more frequently. The joint, which shows repeated bleeding events, is called a target joint, and the ankle and knee joints in the lower limb and the elbow joint in the upper limb are commonly observed to be target joints. Chronic synovitis eventually causes articular cartilage and subchondral bone erosion and degeneration, resulting in a condition called hemophilic arthropathy. The patient does not use the affected limb either consciously or unconsciously due to pain avoidance, and the functional deterioration progresses with increasing intensity in combination with muscle weakness [4]. Synovial resection is one way to break this vicious circle. As mentioned above, synovial tissue, which shows a villous configuration, bleeds easily; however, if such tissue is surgically removed and appropriate hemostasis is maintained in conjunction with coagulation management, joints can be restored to a state in which they do not easily bleed. However, since synovial excision cannot be recommended until

cartilage damage is observed or compatible destroyed joint repair, there are few therapeutic options for highly advanced severe hemophilic arthropathy. Treatment in early-stage hemophilic arthropathy is aimed at providing pain relief by reducing the bleeding frequency; further, this treatment is also applied to delay the progression of arthropathy. However, since the elbow joint does not always receive a high load as compared with the joints of the lower limbs such as the knee joints, if the range of motion can be maintained with little pain or bleeding, synovial ablation is significantly beneficial. Synovial ablation is a good treatment option especially for young people with excellent bone neogenesis and tissue remodeling ability; in this patient population, remodeling may occur on the joint surface depending on the site and stage, and joint repair may also take place to some extent [5, 6].

9. Surgical methods

9.1 Direct surgery

Although different approaches exist for joint surgery, joint synovectomy under direct vision is a common orthopedic surgical procedure and requires no special techniques or instruments. However, post-surgery, synovial membrane remnants may facilitate the recurrence of intra-articular bleeding; surgical removal of the synovial membrane in the joint may also lead to joint contracture caused by postoperative scar formation. In the case of the elbow, if a thorough resection of the synovial membrane in the joint is attempted, the radial head may also have to be removed; both internal and external approaches to the joint may have to be explored. Although there are few opportunities for joint hemorrhage after surgery and hence patient activity increases, there are few things that may improve elbow flexion and extension range. Improvement of forearm restraint can be expected if radial head resection is also performed [7].

9.2 Arthroscopic surgery

Arthroscopy is a surgical procedure that allows surgical access to joints in a minimally invasive fashion and was introduced in the 1940s. Surgical procedures have benefited from advancements in hardware such as cameras, monitors, and surgical instruments. Because there is less damage to the surrounding joint tissues, arthroscopic surgery results in fewer contractures as compared to under-sight surgery. Due to the presence of critically important neural blood vessel bundles surrounding joints, a strong knowledge of anatomy and technical proficiency are required to perform this surgical procedure. However, if done well, synovial resection with arthroscopy can be as effective as or more effective than that performed under direct vision; additionally, as mentioned above, there is little contracture after surgery. Therefore, arthroscopic surgery is recommended for surgical synovectomy of the hemophilic elbow joint [8].

9.2.1 Elbow arthroscopic surgery

The elbow joint has a complicated structure in which the upper and side surfaces of the radius are in contact with the hinge joint (called the arm slider). In order to remove all proliferating synovial membranes in this joint cavity, three parts need to be approached: the anterior, posterior, and the radial parts. It is necessary to create at least two portals for inserting the arthroscope and other instruments such as a shaver. Surgery is performed after the arthroscope and other instruments have been

placed properly. Using the abovementioned portal, instruments such as a shaver and a high frequency cautery/transpiration device are employed for performing the surgery. In hemophilic arthropathy, the synovial membrane appears yellowish brown due to hemosiderin deposition caused by repetitive bleeding; the blood vessels in the synovial membrane proliferate significantly in the acute inflammatory phase and bleed easily. However, if the exposed blood vessels are cauterized intraoperatively, the surgery itself is comparable to a conventional synovectomy. It is impossible to surgically remove 100% of the synovial membrane; at the elbow joint, this membrane often grows around both side margins of the wrist joint and around the radial neck. MRI imaging of the synovial membrane is thus performed before surgery, so that a comprehensive resection of the synovium may be achieved to the extent possible. At the end of surgery, one of the portals is used to indwell a closed-type drain in the joint, and the blood in the joint is aspirated and discharged. The drain is removed at about 48–72 hours post-surgery, which is slightly longer than that for conventional arthroscopic surgery.

10. Perioperative hemostasis/coagulation management in synovectomy

Coagulation factor supplementation is frequently performed before surgery, and the aim is strict hemostasis/coagulation management, so that intra-articular bleeding is prevented during the perioperative period. Synovectomy is also specifically aimed at reducing the frequency of intra-articular bleeding. Perioperative bleeding causes synovial proliferation in the joints leading to recurrent bleeding episodes; hence, it is desirable to adequately replenish coagulation factors while monitoring clotting factors and hemostatic and coagulation parameters.

11. Artificial joint replacement

Indications for artificial joint replacement include (1) late-stage arthropathy, (2) serious disruption in activities of daily living (ADL) due to arthropathy, and (3) adults (epiphyseal line is closed). The three points mentioned above are important for patient selection. For the clinical evaluation of late-stage hemophilic arthropathy, the same criteria as applied for osteoarthritis can be accepted. While effect on ADL is an important selection criterion, ADL parameters are highly subjective. Therefore, it is necessary to discuss before surgery whether the patient's desired postoperative life level can be secured. In adult hemophilia patients, it is necessary to explain that when multiple joints develop terminal arthropathy, multiple joint surgeries need to be performed. Artificial joints are usually installed in those aged 60 years or older, and at this age, re-replacement surgery may not be required. However, in some hemophilia cases, patients are forced to use a wheelchair from the age of 20 years, because of pain from arthritis. While artificial joint replacement surgery in young patients does not address the underlying arthritic condition, this surgery nevertheless becomes a necessity to improve QOL. It is important to note that performing re-replacement surgeries repeatedly is not feasible and performing artificial joint replacement may just postpone the occurrence of joint problems. However, in our opinion, living in a wheelchair in the older age may be an acceptable way of maintaining a patient's QOL, if an active lifestyle is facilitated for the patient during the young-to-mature years. For this reason, it may be better to perform artificial joint replacement even in young patients, based on the case details. The most important reason to perform artificial joint replacement is to eliminate or alleviate pain. Simultaneous synovectomy is also performed for cases with joint

hemorrhage, so as to stop or reduce the number of bleeding events. On the other hand, the knee joint has been reported to show poor improvement in range of motion. For this reason, postoperative rehabilitation is important.

12. Arthrodesis

Arthrodesis involves surgically immobilizing affected joints. By sacrificing the range of motion of the joint, this procedure treats joint pain and intra-articular bleeding. This procedure is performed primarily on the ankle joint. In the natural course of hemophilic ankylosis, the joints appear stark on diagnostic images in the terminal stage. Therefore, surgery to fix joints artificially is not actively carried out, and numerous parameters are monitored while the patient is administered with symptomatic treatment. Arthrodesis has recently been reviewed as a method for treating artificial ankle joints. Although the treatment protocol varies depending on the facility, if only one side presents with terminal arthrosis, the joint function can be compensated by the other healthy side, so that joint fixation is applied. If ankle joints on both sides are candidates for artificial ankle joint replacement, this condition is an indication for artificial ankle replacement.

13. Problems other than hemostasis in joint surgery

13.1 Preoperative examination and anesthesia management

Spinal anesthesia has been conventionally contraindicated as a method of anesthesia in hemophiliac patients, and surgery has been performed with general anesthesia. The reason is that when the spinal venous plexus is damaged at the needle tip of the lumbar puncture needle, if the coagulation is insufficient, hemorrhage is prolonged and may lead to a deep hematoma; the discovery of such a hematoma is liable to be delayed due to the depth of the location. If such a hematoma occurs, there is a high risk for spinal cord injury. With modern hemostatic management methods, it is possible to maintain the levels of coagulation factors adequately while concurrently administering spinal anesthesia, and if persistent subdural anesthesia can be performed, it is effective for postoperative pain management. However, while very few institutions use spinal anesthesia during surgery in patients with hemophilia, most perform surgery with general anesthesia. There is no relevance of hemophiliac status on the choice of anesthetics. However, depending on the type of antiviral drugs used for people infected with HIV, care should be taken because some drugs inhibit the metabolism of anesthetics and increase the required dosage.

13.2 Surgery in HCV- and HIV-infected patients

Some patients who undergo orthopedic surgery (especially that of artificial knee replacement) show co-occurring HCV or HIV infections due to phytotoxicity. While a proportion of patients with successful treatments (e.g., interferon therapy) no longer have HCV infections, many patients show progression to liver cancer or liver cirrhosis due to long disease duration. In contrast, though symptomatic improvement may be achieved with the latest antiviral drugs in HIV-infected patients, a cure is not possible. Particularly with respect to hepatitis C, postoperative death cases are significantly higher among cases characterized as Child classification B, those with low ascites and albumin, and those with thrombocytopenia [9]. Confirmation of these conditions is important for surgical decisions.

13.3 Prevention of deep venous thrombosis (DVT)

Lower extremity artificial joint surgery is one of the risk factors for deep venous thrombosis (DVT), and DVT risk is of particular relevance in hemophilia patients. However, most hemophilia patients undergoing artificial joint replacement surgery are adolescents on anti-inflammatory analgesic therapy and show no other comorbidities that may influence thrombus development. Therefore, the risk of DVT occurrence due to lower extremity artificial joint surgery may be lower than that due to general lower limb prosthesis replacement surgery. However, it was reported that among asymptomatic patients, DVT was detected by lower limb ultrasonography in 10% of cases after surgery, even in patients with hemophilia [10]. A previous report has suggested that in addition to physical methods such as application of elastic stockings and intermittent pneumatic compression, anticoagulation therapy is administered at about half of the facilities where the survey was conducted [11]. Either way, even in patients with hemophilia, physicians must be alert to the development of postoperative DVT, and timely cessation of prescribed bed rest and early rehabilitation are important.

14. Latest findings due to the appearance of half-life extended drugs

The development of coagulation factor preparations is one of the most important factors impacting the prognosis and quality of life of patients with hemophilia. Recent advancements in extending the half-life of drugs using various mechanisms have attracted much attention. Such extended half-life formulations make it possible to reduce the frequency of self-injections even in regular prophylaxis therapy and reduce the frequency of bleeding symptoms (such as bleeding in the joints and muscles). In addition, such advancements not only extend the half-life and improve the stability of the drugs; they also impact patient burden by reducing the number of required hospital visits. Various benefits have been obtained from the use of half-life extended drugs, and this development has brought about major changes in the treatment of hemophilia. However, since half-life extended medicines are short, there is a lack of substantial evidence of the efficacy in perioperative administration regimens. Moreover, the number of cases in which these drugs have been used is too small for inclusion in case report studies. In this regard, we have experienced and reported a case of perioperative management of hemophilia A using efraloctocog alfa (ELOCTATE®) during endoscopic nasal pituitary adenomectomy for growth hormone-producing pituitary adenoma. There are no other reports of the successful use of ELOCTATE (a drug with an extended half-life) in conjunction with the BI method for a major surgery. We summarize below details of the case study [12]. A 28-year-old man was admitted to our hospital due to bulging of the glabella. He had first noticed the bulging of the glabella in 2013. He was aware of the enlargement of his fingers and the size of his shoes since August 2016, and he was now seeking medical attention. He was referred to the department of endocrinology and metabolism at our hospital with suspected acromegaly. A diagnosis of growth hormone-producing pituitary adenoma was made by performing several tests, including a brain MRI and loading tests. Furthermore, we decided to perform endoscopic nasal pituitary adenomectomy at our department of neurosurgery. The patient clinical history included hemophilia A, pediatric asthma, and hypothyroidism.

Hemophilia A was diagnosed as moderate in infancy. The patient reported self-injecting rurioctocog alfa (trade name: ADVATE®) two to three times a week for hemophilia. The final bleeding episode occurred in the left knee joint in April 2013 and required hospitalization for 3 days. Factor VIII inhibitors were not detectable in

the patient's blood. We prepared a regimen for administration of rFVIIIFc in accordance with guidelines for hemostasis treatment for hemophilia patients without inhibitors (Revision 2013, published by the Japanese society of Thrombosis and Hemostasis). At our hospital, the results of factor VIII activity cannot be obtained promptly, so in the perioperative period, we monitored APTT in lieu of factor VIII levels in sera. From day 2 onward, we injected rFVIIIFc intravenously at 2 PM daily and measured APTT and factor VIII activity at 6 AM the following morning (16 hours after intravenous injection). A blood test was conducted to measure APTT and factor VIII activity at 6 AM on surgery day. On the day of the surgery, 4000 IU of rFVIIIFc were intravenously injected at 8 AM (1 hour before leaving the ward for the surgery), and APTT and factor VIII activity were measured again after 15 minutes of intravenous injection (because peak levels of rFVIIIFc in the blood are achieved approximately 15 minutes after intravenous injection). APTT at this time was assumed to be a function primarily of factor VIII activity and was used as the most important index in perioperative control. The surgery began at 10:14 AM and ended at 1:39 PM (3 hours and 25 minutes). The surgery performed was an endoscopic nasal pituitary adenomectomy. The volume of bleeding during the surgery was 150 ml and was in close agreement with the expected volume of bleeding. Prior to surgery, a risk of bleeding from the nasal mucosa was suspected; however, only two mild nasal bleeding events were confirmed and were resolved adequately. The patient was discharged on day 13, on schedule. Thus, perioperative management using drugs with an extended half-life can be applied to control hemostasis/coagulation at the perioperative stage using the BI method even for major surgery, as in the case described above. The advantage of perioperative management by the BI method using half-life extended drugs is that these drugs need to be administered through intravenous injection only once a day, and such a treatment protocol is easy to perform at a hospital. Furthermore, the BI method is also economical as it reduces the amount and thus the cost of the drug, as compared with the CI method using the existing coagulation factor preparations. For perioperative management using extended half-life drugs, we consider that further case studies are necessary to prepare dosing regimens. However, such drugs have the potential to impact not only periodic replacement therapy but also perioperative management in hemophilia patients. For the reasons stated above, we feel that the extended half-life drugs have the potential to significantly impact hemophilia treatment.

15. Possibility of subcutaneously injectable coagulation factor preparations

Another recent advancement in hemophilia drugs is the development of a subcutaneously injectable formulation, which overcomes the need for intravenous injection. The common name of this drug is emicizumab, and the trade name is HEMLIBRA®. The efficacy of emicizumab is characterized as "suppression of bleeding tendency in congenital factor VIII-deficient patients positive for inhibitors against factor VIII." As with other factor VIII drugs and bypass medicines, there are no indications for administration during perioperative period or during sudden bleeding events, and increase in blood emicizumab levels is disallowed. Currently, this drug has been formulated as an intravenous injection and is being used for sudden bleeding events or during surgery in patients who undergo prophylactic replacement therapy with subcutaneous coagulation factor preparations. In the future, it is expected that this drug will also be recommended for use in hemophilia patients who are negative for factor VIII inhibitors. However, currently, this drug is being administered only to patients positive for factor VIII inhibitors. Phase III clinical trials of

the use of emicizumab in surgical cases have been conducted, but the subjects have been limited to those positive for factor VIII inhibitors. Literature evidence of the use of emicizumab during surgery in patients without inhibitors is lacking, and thus comparative assessments cannot be made. There is also no evidence regarding the use of this drug during time of surgery in patients with inhibitors as well. As described above, there is little evidence to support the efficacy of emicizumab administration in perioperative period, and further studies are indicated.

16. Treatment of hemophiliac patients with inhibitors

16.1 Outline

Inhibitors are anti-factor VIII or anti-factor IX allogeneic antibodies generated against factor VIII and factor IX in pharmaceutical preparations as a result of replacement therapy with coagulation factor preparations. When an inhibitor generates, it binds to factor VIII and factor IX, resulting in structural and functional abnormalities. Furthermore, as the clearance is increased by the formation of the antigen-antibody complex, the hemostatic effect of replacement therapy drastically decreases/disappears [13]. Hemostasis therapy is roughly divided into neutralization therapy and bypass hemostasis therapy. And it is chosen mainly based on the severity of bleeding symptoms, the potency and reactivity of the inhibitor, and past medical history.

16.2 Inhibitor phenotype

Inhibitors are measured by Bethesda method [14] based on coagulation single step method. The amount of antibody that inactivates factor VIII or factor IX contained in 1 ml of normal plasma by 50% is defined as 1 Bethesda Unit/ml (BU/ml). Normally, >0.6 BU/ml is judged to be positive for inhibitors. In particular, the Nijmegen method is recommended for measurements around 1 BU/ml [15]. Inhibitor titers are defined as high titer ≥ 5 BU/ml and low titer <5 BU/ml. A high responder (HR) is defined as a case in which an inhibitor of ≥5 BU/ml in the Factor VIII/IX Subcommittee of the International Conference on Thrombosis and Hemostasis. And it is recommended that <5 BU/ml case be defined as low responder (LR) [16]. Inhibitor titers may jump sharply 5–7 days after preparation administration. This is called an anamnestic response. The Japan Society of Thrombosis and Hemostasis Academic Standardization Committee Hemophilia Subcommittee advocates an algorithm for selecting therapeutic preparations depending on the potency of the inhibitor and either HR or LR.

17. Replacement therapy

17.1 Selection criteria for replacement therapy and dosage

The first choice of low titer (<5 BU/ml) inhibitor holding LR with no anamnestic response in the past is a continuation of replacement therapy [17]. To obtain a definite hemostatic effect, add the necessary formulation for inhibitor neutralization and target hemostatic level. The neutralization amount (unit) is theoretically calculated as 40 × weight (kg) × {[100 hematocrit value (%)]/100} × inhibitor titer (BU/ml). Depending on the inactivation pattern of the anti-factor VIII or anti-IX factor activity of the inhibitor, it may not necessarily rise as expected. Therefore, monitoring of coagulation factor activity is desired. Bypass hemostasis therapy

described later is the first choice for HR types that have elevated ≥ 5 BU/ml in the past even at <5 BU/ml, but in case of severe bleeding symptoms or major surgery, replacement therapy is selected. However, in the case of HR, it is practical to plan a hemostasis therapy after the reaction, taking into consideration the appearance of previous immune response after 5–7 days after administration. Usually change to bypass hemostasis therapy. Even when the inhibitor titer is 5–10 BU/ml, it is possible to carry out neutralization therapy with high volumes of Factor VIII and Factor IX preparation at severe bleeding and major surgery.

17.2 Selection of replacement therapy preparation

There are three types of factor VIII (FVIII) preparations that can be used in Japan. They are plasma-derived factor VIII formulation, genetically modified factor VIII, and plasma-derived factor VIII (FVIII)/von Willebrand factor (VWF) complex preparation. There are two types of factor IX preparation that can be used: plasma-derived preparations and recombinant preparations. In some hemophilia A inhibitor cases, it is known that the hemostatic effect of the FIII/VWF preparation exceeds that of the factor VIII preparation. It is clarified that this inhibitor is an antibody which recognizes the factor VIII light chain and suppresses FVIII/VWF binding, and reactivity to FVIII is decreased by the presence of VWF [18].

17.3 Method of administration of preparation

Normally, factor VIII preparation and factor IX preparation are administered in bolus, but continuous administration is also selected at severe bleeding and hemostatic management of major operation. There are no standards for dose administration in inhibitor cases. If the inhibitor is completely neutralized by the initial bolus administration, the coagulation factor activity can theoretically be maintained in the administration example similar to the cases without inhibitor. In practice, however, higher doses are often required.

18. Bypass hemostatic therapy

According to the guidelines published by the Japan Thrombosis Hemorrhagic Society, the first choice when the inhibitor titer ≥ 5 BU/ml is bypass hemostasis therapy except severe bleeding symptoms and hemostasis management during major surgery [17]. Traditionally, activated prothrombin complex concentrates (aPCC) or prothrombin complex concentrates (PCC) were the main body of bypass hemostasis therapy, but bypass hemostasis therapy has greatly advanced after the introduction of genetically modified active factor VII factor formulation (rFVIIa). Sales of PCC preparations adapted for inhibitors have been discontinued. Currently available bypass preparations are three, aPCC (FEIBA®), rFVIIa (NovoSeven®), and blood coagulation factor X factor-activated factor VII (Byclot®).

18.1 Bypass hemostatic therapy preparation

18.1.1 Activated prothrombin complex concentrates (aPCC)

18.1.1.1 Hemostasis management during surgery by aPCC

Conventionally, it was extremely difficult for a variety of reasons to perform hemostasis management at the time of surgery of HR inhibitor cases with

inhibitors of high titer by only aPCC. The main reasons are the uncertainty of the hemostatic effect, expensive medical expenses, thrombosis, and fear of onset of disseminated intravascular coagulation syndrome (DIC), and furthermore, the evidence is low. Many of the cases used aPCC in combination after neutralization therapy with factor VIII and factor IX preparations. However, in conjunction with the increase in patients undergoing surgery by rFVIIa, reports on practical cases with only aPCC have been increasing in recent years. According to a multicenter retrospective study by Negrier et al., aPCC was used for 19 small surgical procedures [19]. The most frequent cases were joint puncture (10 cases), the number of doses was two to six times, and the administration days were in the range of 2–4 days, both of which were effective. The dose was 78–160 units/kg/day. Four cases were used for tooth extraction, three cases were administered twice, one case was administered six times, and the administration period was, respectively, 1 day and 3 days. Four cases were performed in major surgery. The breakdown was knee joint synovectomy, knee arthroplasty, skin muscle formation, and prostatectomy. The dose and duration of aPCC during major surgery differ depending on the operation name. The dose is 120–210 units/kg/day and the administration period is 5–21 days. The dosing regimen after surgical treatment such as subcutaneously implanted central intravenous catheterization procedure ranged from 50 to 74 units/kg one to two times/day; dosing days ranged from 1 to 6 days [20]. In Japan, since aPCC had limitation of use (inhibitor potency $\geq$10 BU/ml, within 3 days of administration), experience of using aPCC in major surgery is small. Since these restrictions have been removed since 2008, surgical therapy using aPCC in Japan could be considered. The number of cases is still small internationally, and it is necessary to standardize on the aPCC administration regimen at the time of surgery in the future.

18.1.1.2 Anamnestic response by aPCC

A fragment of factor VIII is detected in aPCC. Therefore, there are cases in which inhibitor titers are increased by repeated administration of aPCC. This is because aPCC contains the light chain fragment of factor VIII, and it is common in inhibitors of the light chain recognition type in particular [21]. Therefore, in cases that the inhibitor titer does not decrease and the high value is sustained, it is necessary to pay attention to the anamnestic response caused by aPCC. Incidentally, even in cases with this history of reaction, there are cases in which they subsequently decline as a result. In the report of Negrier et al., anamnestic response was seen in 31.5% of the patients, but of which 64.7% had gradually decreased [19].

18.1.2 rFVIIa

18.1.2.1 Hemostasis management during surgery by rFVIIa

rFVIIa is being used not only for small surgical operations but also for moderate or more surgical operations. Lusher et al. collected results on 103 surgical operations totaling 21 cases of major operation, 57 cases of small operation, and 25 cases of suturing relation [22]. According to the report, effective cases were 81, 86 and 92%, respectively, indicating that major surgery is also possible with hemostasis management by rFVIIa. Even in Japan, there are no restrictions on insurance medical treatment, so we have used more experience than aPCC and the number of cases such as large orthopedic surgery including artificial joint replacement surgery is increasing. Schrarer et al. recommended that 90 μg/kg every 2–3 days for 1–2 days, in large

surgery, and, in small surgery, the same amount of administration every 2–4 hours, every 6–7 days and every 6–8 hours 2 weeks [23]. Rodriguez et al. collected 108 cases of orthopedic surgical cases with inhibitor and reported the usefulness of rFVIIa [24]. Eighty cases of orthopedic surgical cases were collected over the period from 2000 to 2006. The initial dose was 120 µg/kg and thereafter administration of 90 µg/kg every 2 hours or 50 µg/kg/hour in continuous administration. Obergfell et al. reported that this regimen is useful [25]. In Japan's guidelines, as in the case of severe bleeding hemostasis therapy, administration is performed every 2 hours for 1–2 days at the time of major operation. Thereafter, they recommend a regimen that gradually extends the dosing interval, for example, every 3, 4, 8, and 12 hours [17]. Because of its short half-life and the fact that thrombin burst is caused by high concentration of FVIIa is considered to be the basis of hemostatic effect, bolus administration is recommended in principle for administration of rFVIIa. However, there are increasing reports that sustained administration therapy is useful, especially when frequent administration is required as in surgical operation [26, 27]. In general administration method, continuous administration is started at 14–16.5 µg/kg/hour after the initial bolus administration of 90–120 µg/kg. Thereafter, the factor VII activity (FVII:C) is administered so as to maintain at least 10 units/ml. However, Ludlam et al. recently encouraged maintaining the trough level of FVII:C at 30 units/ml at a dose of 50 µg/kg/h during major surgery [28].

18.1.3 Mixture of plasma-derived factor VIIa and factor X (MC710)

MC710 is a plasma-derived new bypass hemostatic therapeutic agent developed in Japan, because the effect of FVIIa is enhanced and sustained due to the coexistence of FX (FVIIa:FX = 1:10). According to pharmacodynamic analysis by coagulation waveform analysis conducted in Phase I study, activated partial thromboplastin time (APTT), maximum solidification rate, and maximum coagulation acceleration peaked 10 minutes after MC 710 administration. And it was before administration level 12 hours after administration. Although the enhancing effect of MC710 was not concentration dependent, it was higher than 120 µg/kg of rFVIIa or 50/75 U/kg of aPCC at dose>80 µg/kg [29]. Furthermore, in Phase II clinical trials, efficacy and safety were examined at two doses of 60 µg/kg and 120 µg/kg in patients with inhibitors of six cases. The hemostasis effect was effective and remarkable 8 hours after administration in total nine bleeding episodes. There were no side effects attributable to the formulation [30].

19. Selection of bypass hemostatic therapy preparation

Both current bypass treatment formulations, aPCC and rFVIIa, have been clarified for efficacy in hemostatic therapy for acute bleeding and surgical treatment. However, as to selection of both formulations, it is necessary to comprehensively select the presence/absence of anamnestic response in the past, the risk of thrombosis, and past hemostatic effect. It was revealed that the hemostasis effect between a single dose of aPCC (75–100 Units/kg) and two doses of rFVIIa (90–120 µg/kg) is equivalent to the hemorrhage of the joint [31]. Interestingly, however, cases were found in which there was a difference in hemostatic effect among the preparations. Even in the same case, the difference in the hemostatic effect between both preparations suggests that it is necessary to change to multiple drugs when the first choice preparation is ineffective [32]. For the selection of preparations at the time of surgery, it has been reported that preparations are added ex vivo to the patient's plasma

prior to surgery and the hemostatic effect is judged by rotation thromboelastometry (ROTEM) before operation [33].

20. Bypass hemostatic therapy in special case

20.1 Cases before immune tolerance induction (ITI therapy)

Regarding the effectiveness of ITI therapy, the only statistically proven factor is the potency of the inhibitor at the beginning of ITI. Therefore, the lower the inhibitor titer, the higher the success rate. Recent international clinical studies of ITI also target <10 BU/ml patients [34]. As a rule, rFVIIa is the first choice in cases where anamnestic response occurs with aPCC administration.

20.2 Cases with a history of allergic symptoms

Some patients with hemophilia B with some inhibitors have allergic symptoms for the preparation containing factor IX. Allergic symptoms are often severe and may present anaphylaxis. The essence of allergic symptoms is anti-IX factor IgG (immunoglobulin G), which is said to be particularly IgG1 antibody [35]. The aPCC preparation contains factor IX. Patients who are allergic to factor IX preparation may have similar symptoms to aPCC. For such cases, it is also possible to desensitize by administering a preparation containing factor IX in small amounts [36]. In general, however, the first choice in cases with allergic history is rFVIIa and MC710.

21. Conclusion

Here we summarize the various options available for the perioperative management of patients with hemophilia and also discuss joint surgery, which is an important aspect of treatment of patients with hemophilia. Unlike healthy subjects, patients with hemophilia require special perioperative management. We hope that this manuscript will help in formulating better treatment of patients with hemophilia in the future.

Acknowledgements

Conflict of interest

We do not have conflicts of interest to disclose.

Notes/thanks/other declarations

I would like to thank the coauthors who supported the writing of this chapter and advised me.

Author details

Atsushi Okamoto, Kenta Yamamoto, Go Eguchi, Yoshitaka Kanai, Terufumi Yamaguchi and Yasuhiro Maeda*
Department of Hematology, National Hospital Organization Osaka Minami Medical Center, Osaka, Japan

*Address all correspondence to: ymaeda@ommc-hp.jp

IntechOpen

References

[1] Amano K. Hemostasis Management of the Latest Haemophilia. Tokyo: Medical Plactice 24 Bunkodo; 2007. pp. 2165-2170

[2] Dunn AL, Manco-Johnson M, Busch MT, et al. Leukemia and P32 radionuclide synovectomy for hemophilic arthropathy. Journal of Thrombosis and Haemostasis. 2005;**3**:1541-1542

[3] Medical and Scientific Advisory Council: MASAC Recommendation #194. 2010. Available from: http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=156&contentid=335

[4] Taketani H. Orthopedic treatment for haemophilic arthropathy. Blood Frontier. 2006;**16**:1797-1804

[5] Tanaka Y, Shinohara Y, Narikawa K, et al. Arthroscopic synovectomies combined with reduced weight-bearing using patella tendonbearing braces were very effective for progressed haemophilic ankle arthropathy in three paediatric patients. Haemophilia. 2009;**15**:833-836

[6] Shimada K, Takedani H, Inoue K, et al. Arthroscopic synovectomy of the elbow covered with rFVIIa in a Haemophilia B juvenile with inhibitor. Haemophilia. 2012;**18**:e414-e416

[7] Lofqvist T, Nilsson IM, Petersson C. Orthopaedic surgery in hemophilia. Clinical Orthopaedics and Related Research. 1996;**332**:232-241

[8] Journeycake JM, Miller KL, Anderson AM, et al. Arthroscopic synovectomy in children and adolescents with hemophilia. Journal of Pediatric Hematology/Oncology. 2003;**25**:726-731

[9] Hirose J, Takedani H, Koibuchi T. The risk of elective orthopaedic surgery for haemophilia patients:Japanese single-Centre experience. Haemophilia. 2013;**19**:951-955

[10] Hermans C, Hammer F, Lobet S, et al. Subclinical deep venous thrombosis observed in 10% of hemophilic patients undergoing major orthopedic surgery. Journal of Thrombosis and Haemostasis. 2010;**8**:1138-1140

[11] Hermans C. Venous thromboembolic disease in patients with haemophilia. Thrombosis Research. 2012;**130**(Suppl 1):S50-S52

[12] Okamoto A, Yamamoto K, Eguchi G, et al. Perioperative management of haemophilia A using recombinant factor VIII Fc fusion protein in a patient undergoing endoscopic nasal pituitary adenomectomy for a growth hormone-producing pituitary adenoma. Haemophilia. 2017;**6**:e525-e527. DOI: 10.1111/hae.13347

[13] Shima M. Characterization of factor VIII inhibitors. International Journal of Hematology. 2006;**83**:109-118

[14] Kasper CK, Aledort L, Aronson D, et al. Proceedings: A more uniform measurement of factor VIII inhibitors. Thrombosis et Diathesis Haemorrhagica. 1975;**34**:612

[15] Verbruggen B, Novakova I, Wessels H, et al. The Nijmegen modification of the Bethesda assay for factor VIII; C inhibitors: Improved specificity and reliability. Thrombosis and Haemostasis. 1995;**73**:247-251

[16] White GC 2nd, Rosendaal F, Aledort LM, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the international society on thrombosis and haemostasis. Thrombosis and Haemostasis. 2001;**85**:560

[17] Sakai M, Taki M, Ieko M, et al. Guidelines for hemostasis treatment for congenital hemophilia patients with inhibitors 2013 revised edition. Japanese Journal of Thrombosis and Hemostasis. 2013;**19**:520-539

[18] Inoue T, Shima M, Takeyama M, et al. Higher recovery of factor VIII(FVIII) with intermediate FVIII/von Willebrand factor concentrate than with recombinant FVIII in a haemophilia A patient with an inhibitor. Haemophilia. 2006;**12**:110-113

[19] Negrier C, Goudemand J, Sultan Y, et al. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA Study Group. Factor eight bypassing activity. Thrombosis and Haemostasis. 1997;**77**:1113-1119

[20] Kraut EH, Aledort LM, Arkin S, et al. Surgical interventions in a cohort of patients with haemophilia A and inhibitors: An experiential retrospective chart review. Haemophilia. 2007;**13**:508-517

[21] Yoshioka A, Kamisue S, Tanaka I, et al. Anamnestic response following infusion of prothrombin complex concentrates (PCC) and activated prothrombin complex concentrates (aPCC) in hamophilia A patients with inhibitors. Blood Coagulation and Fibrinolysis. 1991;**2**:51-58

[22] Lusher JM, Roberts HR, Davignon G, et al. A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. rFVIIa Study Group. Haemophilia. 1998;**4**:790-798

[23] Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VIII deficiency. Haemophilia. 1999;**5**:253-259

[24] Rodrigues-Merchan EC, Jd WJ, Wallny T, et al. Elective orthopedic surgery for hemophilia patients with inhibitors: New opportunities. Seminars in Hematology. 2004;**41**(1 Suppl):109-116

[25] Obergfell A, Auvinen MK, Mathew P. Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopedic surgery: A review of the literature. Haemophilia. 2008;**14**:233-241

[26] Schulman S, Bech Jensen M, Varon D, et al. Feasibility of using recombinant factor VIIa in continuous infusion. Thrombosis and Haemostasis. 1996;**75**:32-36

[27] Mauser-Bunschoten EP, Koopman MM, Goede-Bolder AD, et al. Efficacy of recombinant factor VIIa administered by continuous infusion to haemophilia patients with inhibitors. Haemophilia. 2002;**8**:649-656

[28] Ludlam CA, Smith MP, Morfini M, et al. A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: A pharmacokinetic and efficacy evaluation. British Journal of Haematology. 2003;**120**:808-813

[29] Shirahata A, Fukutake K, Mimaya J, et al. Results of clot waveform analysis and thrombin generation test for a plasma-derived factor VIIa and X mixture (MC710) in haemophilia patients with inhibitors—Phase I trial; 2nd report. Haemophilia. 2013;**19**:330-337

[30] Shirahata A, Fukutake K, Takamatsu J, et al. A phase II clinical trial of a mixture of plasma-derived factor VIIa and factor X (MC710) in haemophilia patients with inhibitors: Haemostatic efficacy, safety and pharmacokinetics/pharmacodynamics. Haemophilia. 2013;**19**:853-860

[31] Astermark J, Donfield SM, DiMichele DM, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: The FEIBA NovoSeven Comparative (FENOC) study. Blood. 2007;**109**:546-551

[32] Hayashi T, Tanaka I, Shima M, et al. Unresponsiveness to factor VIII inhibitor bypassing agents during Haemostatic treatment for life-threatening massive bleeding in a patient with haemophilia A and a high responding inhibitor. Haemophilia. 2004;**10**:397-400

[33] Furukawa S, Nogami K, Ogiwara K, et al. Systematic monitoring of hemostatic management in hemophilia A patients with inhibitor in the perioperative period using rotational thromboelastometry. Journal of Thrombosis and Haemostasis. 2015;**13**:1279-1284

[34] Hay CR, Dimichele DM. International immnne tolerance study: The principal results of the international immune tolerance study: A randomized dose comparison. Blood. 2012;**119**:1335-1344

[35] Sawamoto Y, Shima M, Yamamoto M, et al. Measurement of anti-factor IX IgG subclasses in haemophilia B patients who developed inhibitors with episodes of allergic reactions to factor IX concentrates. Thrombosis Research. 1996;**83**:279-286

[36] Shibata M, Shima M, Misu H, et al. Management of haemophilia B inhibitor patients with anaphylactic reactions to FIX concentrates. Haemophilia. 2003;**9**:269-271