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

4,300
Open access books available

117,000
International authors and editors

130M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the 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
Chapter

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.
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 hemophilic 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 efralocotocog 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