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Implantoprosthetic rehabilitation of a patient with severe form of hemophilia B: a case report

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Abstract

The preparation of patients with hemophilia before surgical operations and dental procedures constitutes a significant clinical challenge. This article presents the implantoprosthetic rehabilitation of a patient with severe hemophilia B (factor IX activity < 1%). The patient was prepared for the surgical procedure with recombinant factor IX concentrate (Rixubis) during the clinical surgery study. Tooth extraction and the implantation of four dental implants in the mandible were planned: one dental implant of 3.7 mm diameter and 10 mm length in the place of tooth 35, and another of 3.2 mm diameter and 10 mm length in the place of tooth 37. The next two implants were implemented 1 month later: one implant 3.7 mm in diameter and 10 mm in length in the place of tooth 46, and another implant 3.2 mm in diameter and 10 mm in length in the area of tooth 44. Appropriate substitution of the missing coagulation factor, together with the use of local hemostatic therapy, allowed dental implantation to be performed without excessive blood loss in this patient with severe hemophilia B.

Keywords:
hemophilia B, dental implant, implantoprosthetic rehabilitation, Rixubis

Introduction

Hemophilia B is the third most frequently reported (1/30,000 male neonates) congenital bleeding disorder in Poland [1]. Hemophilia B is a recessive, X-linked congenital bleeding disorder caused by the deficiency of clotting Factor IX (FIX) in plasma due to genetic mutations on the FIX gene. The main symptoms related to severe hemophilia B are bleeding into large joints, leading to the so-called hemophilic arthropathy, and disability of the musculoskeletal system. Hemophilia is also associated with bleeding into the temporomandibular joint (TMJ), causing their gradual degeneration and dysfunction, observed mainly in the form of ankylosis, along with various degrees of mandible movement limitations [2]. The type, severity, and frequency of intra-articular bleeding depend on the level of activity of the deficient clotting factor. There are three main types of hemophilia B: mild, moderate, and severe. Severe hemophilia B is diagnosed when the activity of FIX is < 1% [3] and is characterized by spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge. A moderately severe form of the disease is sometimes diagnosed with an activity level of FIX ≤ 2%.

The cornerstone of hemophilia B therapy is the substitution of FIX. It can be applied as an episodic ("on demand") treatment or as a regular continuous treatment (prophylaxis). The most serious complication of substitution treatment is the development of alloantibodies (inhibitors) to FIX, which occurs in about 1%-3% of hemophilia B patients and requires therapy with bypassing agents for the treatment of bleeding episodes [4]. Currently, the standard substitutive treatment for hemophilia B is based on two types of FIX concentrates, plasma derived and recombinant, obtained through genetic engineering techniques [5]. Hemostasis management should be planned for dental extraction or surgical procedures performed within the oral cavity of patients with severe hemophilia B; in addition, an hematologist should also be consulted and FIX substitution provided. Prophylaxis against bleeding related to other surgical or dental procedures also includes the use of antifibrinolytic agents, such as tranexamic acid and e-aminocaproic acid, both in the form of systemic and topical preparations [4, 6]. Other hemostatic agents, such as porcine absorbable gelatin sponges, collagen sponges, cellulose platelet gels, thrombin preparations or increasingly popular fibrin glues, available both in the dry and in the liquid form, can also be used as topical treatment to prevent hemorrhage [7].

Improved control of bleeding facilitated by efficient hemostatic treatment makes it possible for a wide range of surgical procedures to be performed in patients with hemophilia B without inhibitors, including aesthetic procedures within the field of oral surgery and implantology [8, 9]. This greater accessibility of aesthetic procedures increases not only the comfort but also the quality of life of patients with hemophilia.

The aim of this paper is to present the case of an implantoprosthetic rehabilitation performed in a patient with severe hemophilia B. The surgical procedures were performed after infusion of recombinant FIX (BAX 326) during the clinical surgery study. BAX 326 was registered in the European Union in 2014 under the trade name of Rixubis (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003771/human_med_001830.jsp&mid=WC0b01ac058001d124) for treating and preventing hemorrhage in patients suffering from hemophilia B in all age groups.

Case study

Patient S.D., a 45-year-old man with severe hemophilia B, reported to the dental office in March 2013 to replace teeth and to undergo

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prosthetic reconstruction of the lower dental arch. The patient was enrolled into the Rixubis surgery clinical study, aimed at evaluating the hemostatic effectiveness and safety of the recombinant FIX concentrate Rixubis in patients with severe or moderately severe hemophilia B who undergo emergency or scheduled surgical operation, invasive diagnostic procedures, or dental procedures.

The patient was scheduled to have the root of tooth 45 extracted and to have implants introduced in locations corresponding to teeth 35, 37, 46, and 44 (Fig. 1). After a period of 6 months, implant osseointegration and implant exposure were to be evaluated by pantomographic X-ray. This was to be followed by prosthetic reconstruction.

In March 2013, the clotting factor Rixubis was infused, and the root of tooth 45 was extracted under local anesthesia. The tooth socket was curetted, a gelatin sponge was placed (Spongostan), and the wound was sutured with dissolvable sutures. Proper hemostasis was obtained, with blood loss measuring approximately 2 ml. The patient was asked to rinse his mouth with tranexamic acid (Exacyl) preparation (10 ml every 6 hours), as well as to use oral tablets of Exacyl at a total dose of 2 g in two divided doses.

In October 2013, following the infusion of Rixubis at a dose sufficient to attain 130% FIX activity, the mucoperiosteal flaps were incised and detached, and two implants were inserted in the area surrounding teeth 35 and 37: one implant being 3.7 mm in diameter and 10 mm in length (tooth 35) and the second 3.2 mm in diameter and 10 mm in length (tooth 37). The wound was rinsed and closed off. The procedure was performed under local anesthesia. No drains were introduced. The blood loss anticipated prior to the procedure was 7-10 ml. The true blood loss during the procedure was assessed at 6 ml, 3 ml per tooth. No bleeding or inflammation was observed in the operated area in the patient during the postoperative period. In agreement with the study protocol, the patient received a daily dose of 4418 IU FIX for the next 13 days and until complete healing of the wound.

The next two implants were implemented a month later in November 2013, with the FIX level up to 145%. The procedure was performed under local anesthesia. The mucoperiosteal flaps in the area surrounding teeth 46 and 44 were incised and detached, and two further implants were inserted: one with a diameter of 3.7 mm and length of 10 mm (tooth 46); and another with a diameter of 3.2 mm and length of 10 mm (tooth 44). The wound was rinsed and closed off. No drains were introduced. The anticipated blood loss was 7-10 ml. The true blood loss during the procedure was assessed as 6 ml, 3 ml per tooth. No bleeding or inflammation was observed in the operated area after the procedure. According to clinical study requirements, the patient received Rixubis (in daily doses of 4500 IU–5700 IU) for 8 days after surgery until complete healing of the wound was achieved. On the sixth and eighth days following the surgery, the hemostatic effectiveness of the factor was assessed as excellent.

The patient came to the Maxillofacial Surgery Clinic once again in May 2014, 6 months after the final implantation procedure to have the implants inserted in the mandible at teeth 46, 44, 35, and 37. The patient had previously been prepared in the Hematology Department, where the tested FIX was infused. During the examination, the condition of the patient was determined as good, while the X-ray image revealed that implant healing was progressing as expected. After obtaining the results of the activated partial thromboplastin time (APTT) (30.4 seconds) and FIX activity (99%), the surgical procedure was initiated. The anticipated blood loss equaled 5-10 ml. The implants inserted in the area of teeth 46 and 44 were exposed, and healing screws were introduced with minimal blood loss (about 1 ml). The whole procedure lasted 10 minutes. The procedure was performed under local anesthesia. No drains were placed. The

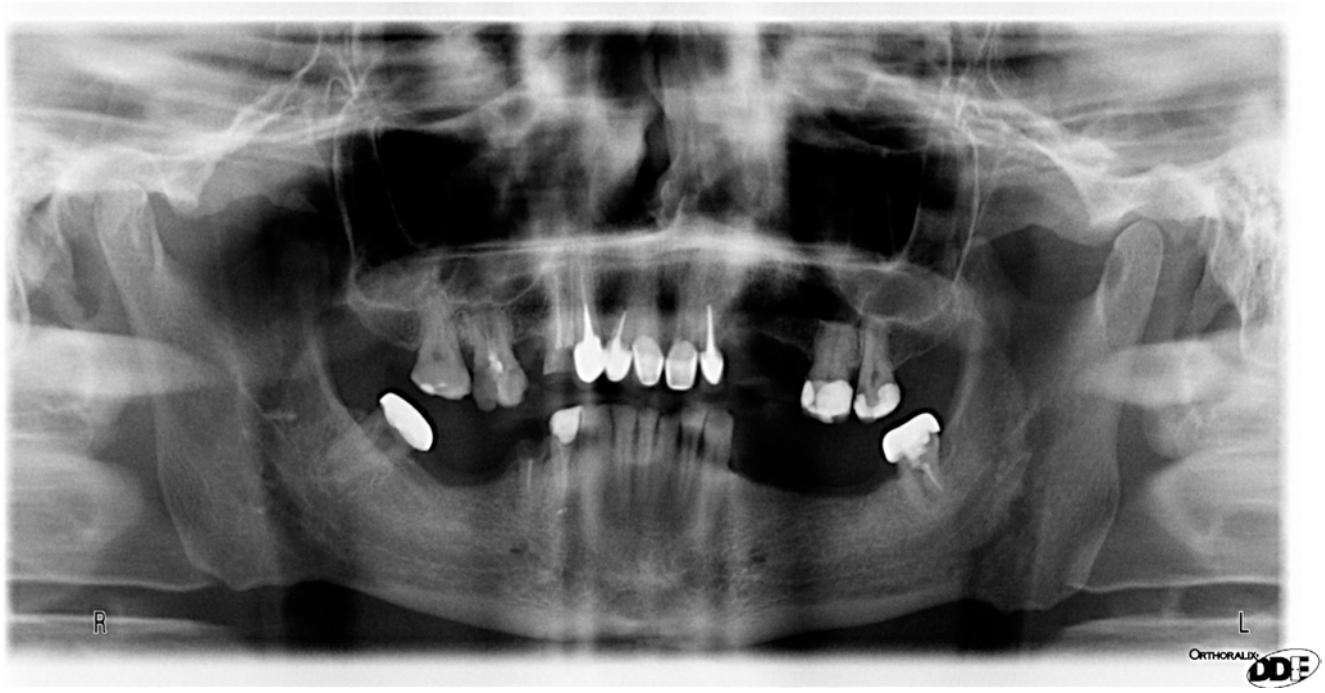

Fig. 1. Orthopantomogram of patient S.D. before implantoprosthetic rehabilitation

implants introduced in the areas of teeth 35 and 37 were inserted, also under local anesthesia, and healing screws were introduced. The procedure lasted 14 minutes, and the blood loss reached about 1 ml. No drains were placed in this case (Fig. 2). One dose of Rixubis was administered on an ambulatory basis the next day.

The effectiveness of Rixubis was evaluated as excellent in both cases. The procedures used to insert the implants in the mandible were uncomplicated, with no excessive bleeding: the blood loss was about 2 ml, and no additional doses of clotting factor were required. The patient did not report any adverse symptoms, and no additional medication was needed to be administered. After the procedure, the patient was transferred to the Hematology Department for further care. The patient had control visits every 6 months in the outpatient clinic, the last one being on January 2017. No adverse or unexpected symptoms related to the implants were recorded.

Discussion

The preparation of patients with hemophilia before surgical operations and dental procedures, particularly prior to implant and prosthetic rehabilitation, constitutes a significant clinical challenge not only for surgeons but also for dentists and hematology specialists. In the case of procedures intended to introduce dental implants, correct hemostasis is crucial for the proper course of the osseointegration process. Appropriate bleeding control is also an important factor in case of tooth extractions and other surgical procedures performed within the oral cavity. Preparing patients before surgical procedures associated with disrupting the soft tissue depends on the extent of the scheduled procedure, as well as the severity of hemophilia and the possible presence of inhibiting alloantibodies (inhibitors). As far as extensive dental procedures are concerned, it is recommended to check the FIX activity level before surgery, especially in severe hemophilia B cases. Patients with severe hemophilia may suffer from extensive hemorrhage following tooth extraction and other dental procedures, not only during but even 2-5 days after surgery [4].

The most important stage of the preparation for invasive surgeries in severe hemophilia B patients is the administration of proper doses of FIX on a standard basis. The required dose is calculated by multiplying the required increase in FIX activity by the body weight of the patient [10, 11]. For major surgeries, FIX levels should not fall below 80%-100% of normal until wound healing is achieved [11]. In the patient described herein, Rixubis study procedures required the drawing of a blood sample for the determination of FIX activity, followed by the administration of a loading dose of Rixubis sufficient to raise the level of FIX in plasma to at least 80%–100% of normal, as introduction of implants is qualified as major surgery. The required FIX units were calculated according to the following formula using the subject's most recently determined, individual incremental recovery: Required units = body weight (kg) × desired rise in factor IX (%) (IU/ dl) × {reciprocal of observed recovery}.

After surgery, the targeted levels of FIX were 80%-100% until adequate wound healing was observed and then 30%-60% for at least another 7 days. Intraoperative and postoperative blood losses were measured at the end of each procedure and then compared with the estimated volume of the expected average and maximum blood loss, as predicted preoperatively by the operating surgeon. In the presented case, the true blood loss was always significantly lower than expected, and no drains were needed during surgery. In the case of our patient, the hemostatic effectiveness of Rixubis was judged as excellent at all studied time points and in all evaluated procedures. No side effects, particularly thrombotic events, were seen after the administration of Rixubis.

The available literature provides only a few reports on implant and prosthetic rehabilitation in patients with hemophilia B [8, 9].

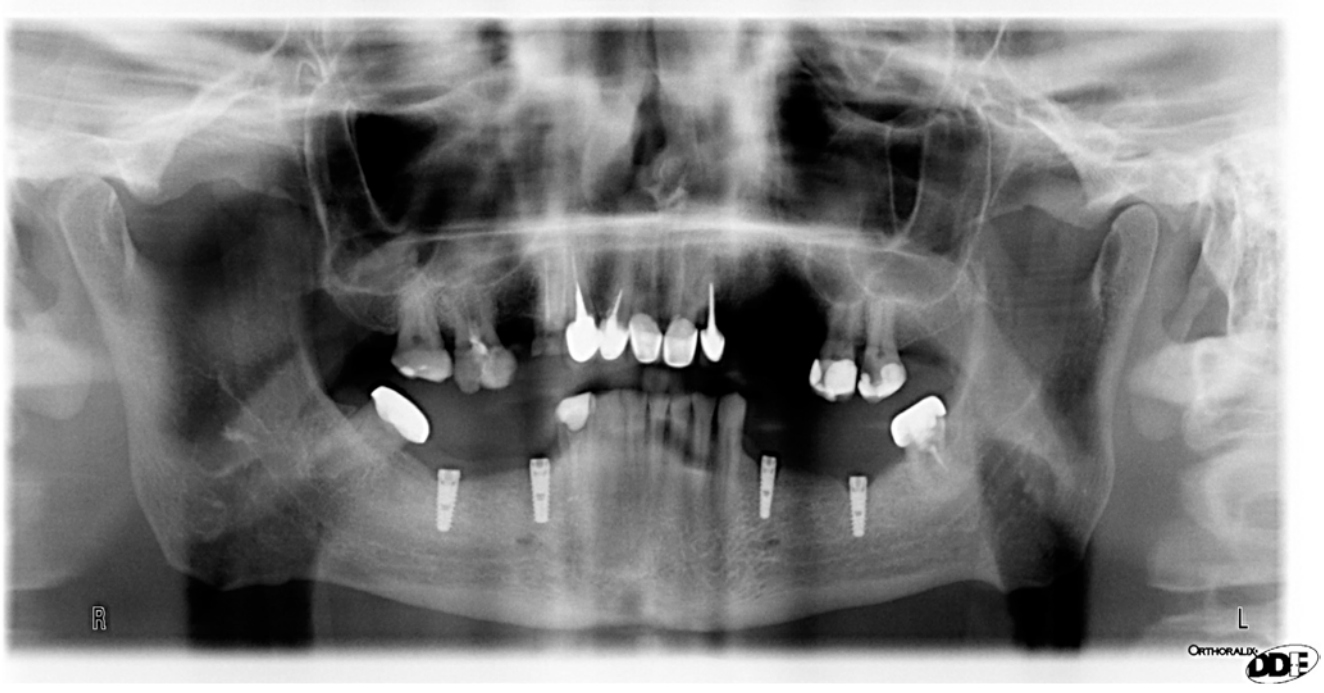

Fig. 2. Orthopantomogram of patient S.D. after final implantation procedure

This is because these patients undergo these procedures very rarely, due to the fear of excessive bleeding and a reluctance to encounter the poorer intraoperative conditions connected with limited mandibular movement caused by temporomandibular joint ankylosis [8]. Significant blood loss into the surgical site hinders the course of implant osseointegration and impairs therapeutic results (primary and secondary stabilization), which increases the risk of the dental implants being lost.

The cases presented in existing literature concern patients with hemophilia A and with the moderate form of the disease [8, 9]. In both cases, the authors obtained satisfactory aesthetic results with little blood loss, both during the intraoperative and the postoperative periods. With regard to the present patient with severe hemophilia B, both aesthetic and functional results were satisfactory, with minimal intraoperative and postoperative bleeding.

In conclusion, the use of Rixubis, along with the use of appropriate local hemostatic therapy, in this severe hemophilia B patient enabled dental implantation without excessive blood loss, thus increasing the chance of proper implant healing as well as allowing for an appropriate functional and aesthetic outcome to be achieved.

Conflict of interests

None.

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