Case Study

# Management of Patients with Hemophilia in Oral Surgery

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**Abstract:**

Management of patients with hemophilia in oral surgery. Hemophilia is an X-linked recessive disorder caused by a deficiency in blood coagulation factors. It occurs more commonly in males. There are 2 types of hemophilia, namely hemophilia A and hemophilia B. Hemophilia A, accounts for about 80% of the cases, occurs due to factor VIII deficiency, while hemophilia B is a factor IX deficiency. The bleeding frequency and severity in hemophilia are usually associated with plasma levels of factor VIII and IX. There are no contraindications to oral surgery for hemophiliac, but it requires certain preparation, both in clinical expertise and appropriate laboratory support. The aim of this paper is to provide knowledge in the management of oral surgery in patients with hemophilia. Two hemophilia patients underwent dental extraction. In the first case, a 14-year-old boy with hemophilia A performed dental extraction under general anesthesia; prophylactic Factor VIII 1500 IU and post-action bleeding stopped after the administration of Factor VIII 1500 IU and tranexamic acid injection. In the second case, 7-year-old boy with hemophilia B performed dental extraction under local anesthesia, factor IX 1000 IU prophylaxis and bleeding after the procedure stopped after the administration of Factor IX 1000 IU, tranexamic acid injection, FFP transfusion, and Factor VIIa. Dentists can perform oral surgery in hemophilia patients by considering the provision of anti-hemophilia factors that is suitable as prophylaxis and therapy in the management of bleeding due to oral surgery.

**Keywords**: dental extraction, hemophilia A, hemophilia B, haemostasis

## Introduction

The most common coagulation abnormalities other than von Willebrand's disease are hemophilia A and hemophilia B. Hemophilia A is an X-linked recessive disorder caused by deficiency or dysfunction of factor VIII (FVIII), while hemophilia B occurs due to factor IX deficiency or dysfunction (FIX). The incidence of hemophilia is 1 per 5,000 live male births. FVIII deficiency occurs in 80-85% of hemophilia cases, whereas FIX deficiency occurs in 15-20% of the cases.[1]

Hemophilia is usually suspected in patients who have history of easy bruising in early childhood, spontaneous bleeding (especially in joints, muscles, soft tissue) or prolonged bleeding due to trauma/surgery.[2] Routine blood tests may be normal with prolonged activated partial thromboplastin time (APTT). The definitive diagnosis can only be determined by examining the levels of FVIII or FIX. The risk of bleeding increases when FVIII or FIX levels decrease.[3]

There are no contraindications to oral surgery in hemophiliacs but special preparation is required in surgical procedures, both in terms of clinical expertise and laboratory examination results that meet the criteria for surgery. This paper reports the management of tooth extraction in patients with hemophilia A and hemophilia B.

## CASE REPORT

### Case 1

A 14-year-old boy came to the Oral Surgery Clinic with complaints of left and right lower back cavities and often pain. The patient had the history of prolonged bleeding in the temples after falling at the age of 6, so that he had to be taken to the hospital for treatment, and then he was diagnosed with Hemophilia A. The patient was

routinely controlled at pediatric outpatient clinic. Family history shows that there are other family members who also suffer from hemophilia A.

Facial examination was symmetric; cheeks, edge of the jaw, and lips with no abnormalities; salivary and lymph glands were not palpable. The intraoral examination of teeth 47, 36, 37 were with gangrenous pulp and tooth 63 persistence. The mucosa, gingiva, tongue, and floor of the mouth were within normal limits (Figure 1). Panoramic X-ray showed teeth 36, 37, 47 with extensive cavity and a round-shaped radiolucent with a firm border <1 cm in diameter which showed the presence of periapical granuloma in teeth 36, 37, 47 (Figure 2). Routine blood laboratory tests were within normal limits, prolonged APTT, and the Factor VIII level was 9.9%.

(a) (b)

Figure 1. The clinical condition of the patient's oral cavity. (a) Tooth 63 persistence; (b)teeth 47, 36, 37 pulp gangrene.

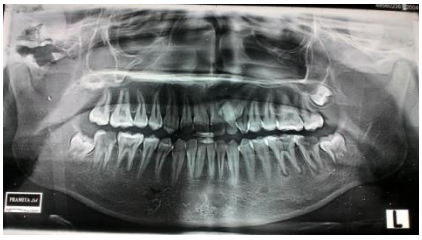

Figure 2. Panoramic X-ray of teeth 36, 37, 47 with broad cavities and round radiolucent appearance with a clear boundary 1 cm in diameter.

The patient was planned for dental extraction 63, 36, 37, 47 under general anesthesia. Preoperative preparation included consultation to the anesthesiologist and hematologist to prevent or minimize postoperative complications. The patient's anesthesia status was ASA II with hemophilia. The diagnosis from the hematologist was Hemophilia A and it was planned to give preoperative administration of FVIII 1500 IU, FVIII 1500 IU half an hour after the surgery started, and FVIII 1500 IU as a maintenance

dose every 12 hours postoperatively. Three days before the surgery, the patient was treated with a 500 mg Amoxicillin every 8 hours and 500 mg Tranexamic Acid every 8 hours, orally.

On the day of the surgery, FVIII 1500 IU was given preoperatively and 1500 IU half an hour after the surgery began. At the anesthesia stage, the extraction of tooth 63 was done atraumatically, continued with teeth 47, 36, 37 extractions and granulation tissue under the socket that could prolong the bleeding was taken. The socket was irrigated and filled with local hemostatic agents, then sutured with a simple interrupted method. Postoperative medications were Ampicillin 500 mg every 6 hours, Dexamethasone 5 mg every 8 hours, Paracetamol 500 mg every 8 hours, Tranexamic acid 500 mg every 8 hours, and FVIII 1500 IU every 12 hours, intravenously.

On the first day after the surgery, the patient's general state was good; there was no bleeding in the gums and minimal pain. Injection drugs were stopped, then the patient got discharged from the hospital. Medicine taken home were Amoxicillin 500 mg every 8 hours, Paracetamol 500 mg if needed, and Tranexamic acid 500 mg every 8 hours, orally for 5 days.

The patient had no complaints for the follow up 1 week after the surgery. Intraoral examination showed good wound healing and no swelling, infection or bleeding (Figure 3).

Figure 3. Postoperative intraoral clinical condition.

**Case 2**

A 7-year-old boy was consulted by a Pediatrician to the Oral Surgery department with gum bleeding for the past five days with luxation on lower front teeth and upper left posterior teeth. The patient received intravenous FIX 1000 IU every 24 hours, intravenous Tranexamic acid 250 mg every 8 hours, and Paracetamol 250 mg every 8 hours, orally. The patient has been diagnosed with hemophilia B for 5 years and routinely receives Factor IX twice a month. For the previous dental health history, the patient had a tooth extraction 2 months ago at Solo Government Hospital under local anesthesia and the suturing was without bleeding complications. There are also family members who suffer hemophilia B.

Facial examination was symmetric; cheeks, edge of the jaws, and lips were symmetric with no abnormalities; salivary and lymph glands were not palpable. In the intraoral examination, blood clot appeared on the cervical teeth 65; gangrene radix on teeth 55, 54, 53, 63, 65, 85; rampant caries on teeth 71, 81, 84; 3$^{rd}$ degree luxation on teeth 65, 71, 81 with partial eruption teeth of 25, 31, 41. The mucosa, gingiva, tongue, and floor of the mouth were within normal limits (Figure 4). Routine blood laboratory tests were within normal limits, with prolonged APTT.

(a) (b)

Figure 4. Clinical conditions of the oral cavity showed blood clot on tooth 65.

Luxation teeth on 65, 71, 81 caused gum bleeding and it was planned for dental extraction under local anesthesia. Preoperative preparation was carried out together with the pediatric department for factor replacement therapy. The patient was given FIX 1000 IU 30 minutes before the procedure. After tooth extraction, the dental sockets were sutured, then the periodontal pack was applied. Medications were continued with intravenous FIX 1000 IU every 24 hours, intravenous Tranexamic acid 250 mg every 8 hours, and Paracetamol 250 mg every 8 hours, orally.

One day after the procedure, the patient still complained about gum bleeding from the extraction site even though it was already pressed with gauze. Intraoral examination showed blood seepage in gingival sulcus of 65 site; there were no post-extraction bleeding on 71, 81 site. The patient was instructed to bite the gauze tampon containing local hemostatic.

Three days after the procedure, there were still bleeding from the tooth socket area 65, 71, 81 and there were residual roots of tooth 65. Then, the extraction of the remaining roots of tooth 65 was done. The patient was given Factor IX 1000 IU 30 minutes before the procedure. The 65 tooth socket was filled with local hemostatic material, then had figure of eight suture with absorbable yarn (Figure 5). Medications were continued with intravenous FIX 1000 IU every 24 hours, intravenous Tranexamic acid 250 mg every 8 hours, and Paracetamol 250 mg every 8 hours, orally.

The fourth day of treatment, the patient's general condition was good and there was no bleeding from tooth socket 65, 71, 81. The patient was still observed and treated with intravenous FIX 500 IU every 24 hour, fresh frozen plasma (FFP) infusion 250 ml every 24 hours, and intravenous tranexamic acid 250 mg every 8 hours.

The ninth day of treatment, the patient complained of bleeding from the extraction area. The patient was instructed to bite the gauze tampon. Then, the factor inhibitor (Bethesda test) was examined and medications were continued.

(a) (b)

Figure 5. Intraoral clinical condition showed tooth socket 65 post extraction.

After 12 days of treatment, blood seepage reappeared from the tooth extraction socket. Intraoral examination showed bleeding and blood clot in 65 tooth socket and loose stitch knot in socket 65. Then, dental socket 65 was sutured with FIX 1000 IU given 30 minutes earlier. After the procedure, the patient got intravenous Tranexamic acid 250 mg every 8 hours and FFP transfusion 150 ml every 18 hours. PRC transfusion was also given to treat anemia.

On the 20$^{th}$ day of treatment, intraoral clinical examination showed bleeding from tooth socket 65. OPG X-ray showed gangrene radix on teeth 55, 54, 53, 63, 85; and rampant caries on tooth 84 (Figure 6). Bleeding came from the tooth socket that had been removed previously, not because of a tooth root that was left behind or sharp tooth parts and there was no indication for immediate other tooth extractions. Bethesda test showed inhibition of FIX. The patient was given a vial of Factor VIIa every 2 hours for 5 times to treat the bleeding.

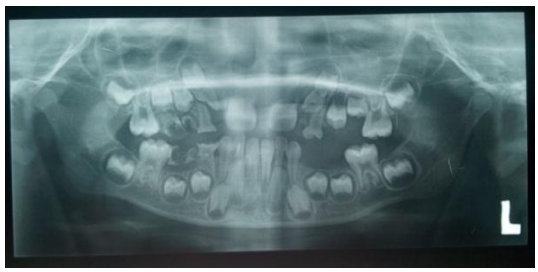

Figure 6. OPG X-ray showed mix dental period, teeth 55, 54, 53, 63, 84, 85 multiple pulp gangrene.

On the 28th day of treatment, the patient's general condition was good and there was no bleeding or infection (Figure 7b). The patient got discharged with medication; Tranexamic acid 250 mg every 8 hours orally for 3 days. There were no complaints in the follow up at the outpatient clinic. Intraoral examination showed good wound healing and no swelling, infection or bleeding.

(a) (b)

Figure 7. (a) Intraoral clinical condition showed dental socket 65 (a) after suturing 12th day; (b) Intraoral clinical condition showed dental socket 65 (b) after treatment of the 28th day.

**Discussion**

Hemostasis is the body's mechanism to stop the bleeding. Normal hemostasis can be divided into two stages, primary hemostasis and secondary hemostasis. In the primary hemostasis, the vascular component and platelet component play the role. Primary hemostasis occurs immediately after injury and results in the formation of platelet plugs which functions to close the injury in blood vessel wall. However, without secondary hemostatic processes, these platelet plugs can disappear immediately from the surface of the blood vessel wall when there is an increase in blood flow in the damaged vessels. Secondary hemostasis involves a series of plasma proteins which interact to form cross-linked fibrin to help stabilize the initial platelet plug. Factor VIII and FIX circulate in the blood as non-active precursors which become active during injury as a part of secondary hemostasis. Abnormalities in patients with hemophilia are the

inability to activate Factor X, which is a derivative of FVIII and FIX, so it can inhibit the formation of thrombin and fibrin to stabilize early platelet plugs.[4]

Hemophilia is classified according to FVIII or FIX levels in the blood, which are mild (5-40%), moderate (1-5%) and severe (<1%).[2] Patients with mild hemophilia do not usually experience spontaneous bleeding. Patients with moderate hemophilia may experience excessive bleeding after trauma, surgery, or tooth extraction and there may also be bleeding in the joints or muscles after minor injuries. Patients with severe hemophilia will experience spontaneous bleeding in the joints and muscles and severe bleeding after injury or surgery.[5]

Patients with hemophilia have a higher risk of secondary bleeding after surgery in the oral cavity. Good management between dentists and hematologists is needed to prevent excessive bleeding. The two cases presented illustrate the challenges in the management of tooth extraction in hemophilia patients. Both of these patients needed advance management with blood clotting factor replacement therapy to overcome prolonged bleeding after tooth extraction. International guidelines strongly recommend the use of blood clotting factor replacement therapy for all invasive surgical interventions. The World Federation of Haemophilia (WFH) recommends the use of factor concentrates to cryoprecipitate or fresh frozen plasma as replacement therapy in hemophilia patients.[6] The successful management of oral surgery in hemophilia patients is related to the administration of blood clotting factor replacement therapy, anti-fibrinolytic agents and local hemostatic procedure.

Blood clotting factor replacement therapy is the main therapy in patients with Hemophilia A or B. The substitution of this clotting factor is done intravenously. Generally, for major surgery, FVIII or FIX must be corrected up to 80% -100% just before surgery and maintained at least 50% for 5-14 days after surgery. Patients who

require procedure with general anesthesia must prepare additional FVIII or FIX to anticipate bleeding due to endotracheal intubation. In tooth extraction, the level required of FVIII or FIX is 50% -70% before surgery and maintained at 50% for 5-7 days after surgery. One FVIII unit per kilogram of body weight can increase FVIII levels in the blood for about 2%, while giving one FIX unit per kilogram of body weight can increase plasma FIX levels for about 0.8% in adults and 0.7% in children.[5,7] Decisions in administering blood clotting factor replacement therapy must be made together with the hematologist so it can meet the individual needs of the patients based on the severity of hemophilia, the level of trauma, and the dental treatment plan.[8]

The most important thing in blood clotting factor replacement therapy is the time of administration because the concentration of this replacement clotting factor will decrease. In these both cases, FVIII and FIX were given before the tooth extraction procedure began. The FVIII or FIX should be given in 10-20 minutes before the procedure, because the concentration level can decrease if they are given too early.[5] The maintenance dose of FVIII is given every 12 hours in hemophilia A and FIX is given every 24 hours in hemophilia B because of the short half-life. In general, FVIII has 6-16 hours half-life and FIX has 14-27 hours half-life.[5]

In the first case, bleeding after tooth extraction could be treated with blood clotting factor replacement therapy (FVIII), but in the second case, the patient did not respond to the blood clotting factor replacement therapy marked by continuous bleeding. This happened because the patient had factor IX inhibitors. In hemophilia, inhibitors are often unnoticed and generally found in uncontrolled bleeding or accidentally found during routine examinations. The presence of inhibitors does not change the type, frequency, or severity of bleeding, but inhibitors cause uncontrolled bleeding.[2,9]

The presence of inhibitor factors is the most serious complication in hemophilia because it increases morbidity and decreases quality of life. Hemophilia with inhibitor factors has IgG antibodies that neutralize blood clotting factor activity. These inhibitors develop in >30% of hemophilia A and about 2% -5% of hemophilia B.[4] Risk factors for inhibitor formations include the genetic, race, age at the first replacement clotting factors therapy, type of hemophilia, type of replacement clotting factor product, duration of exposure, and therapeutic intensity. Inhibitors more often occur in severe hemophilia than moderate and mild types of hemophilia.[4,1] The inhibitor level in hemophilia patients is calculated by the Bethesda test and clinically classified into low and high responders inhibitors. About 25%-40% of hemophilia with inhibitors include low responders (titers <5 Bethesda units [BUs]), bleeding can be treated by increasing the number of replacement clotting factors. While 60% -75% of hemophilia with inhibitors including high responders inhibitors (≥5 BU) can be given bypassing activity inhibitors (recombinant factor VIIa (rFVIIa) and prothrombin complex concentrates).[2,4,10] Postextraction bleeding in the second case could be treated after recombinant factor VIIa administration.

Antifibrinolytic agents are used in conjunction with clotting factor replacement therapy. Tranexamic acid is one of the synthetic derivative antifibrinolytic agents of the amino acid lysine or analog lysine, which can be given orally or intravenously. Structurally similar to lysine, it can inhibit the site of lysine-plasminogen binding to fibrin. Administration of antifibrinolytic agents stabilizes fibrin blockage. The dose of Tranexamic acid is 20-25 mg/kg (maximum 1.5 g) orally or 10 mg/kg (maximum 1 g) intravenously every 8 hours.[1,11] In this case report, the patients were given Tranexamic acid to prevent postoperative bleeding.

Local hemostatic procedure is needed to reduce bleeding after tooth extraction in hemophilia patients. In addition to direct emphasis on gauze tampons and minimal trauma of dental extraction procedure, the application of local hemostatic agents can help minimize the bleeding.[7,12,13] Gelatin sponge can be placed in a tooth socket to help the hemostasis. Oxidized cellulose is a synthetic material that provides a framework for blood clot formation and helps hemostasis, but it has to be used carefully because of the acidic pH content that can irritate dental sockets.[11] Wound suture is used to repair gum flaps, stop bleeding, and prevent postoperative wound disorders due to food scraps.[14] Brewer reported a simple study where sutures were not used routinely and there was no significant increase in post-extraction bleeding. Non-resorbable and resorbable stitches can be used by the operator's discretion. If non-resorbable sutures are used, a postoperative follow up is required and there is a possibility of bleeding when the suture is removed.[12]Resorbable material can carry the risk of infection which can delay healing.[15]

The use of antibiotics aims to reduce the risk of infection that can cause secondary bleeding.[13,14] The analgesic drugs that should be avoided are non-steroidal anti-inflammatory drugs and aspirin because they could affect the platelet function. As a safe alternative, paracetamol, oxycodone and morphine can be used to prevent postoperative pain.[12,16]

**Summary**

Two hemophilia patients who underwent oral surgery performed well. In the first case, bleeding after tooth extraction stopped after the administration of 1500 IU FVIII and tranexamic acid. In the second case, bleeding after the procedure stopped after the administration of 1000 IU FIX, tranexamic acid, FFP, and Factor VIIa transfusion. Dentists can perform oral surgery in hemophilia patients by considering of giving a

suitable clotting factor substitution as prophylaxis and therapy to control bleeding due to oral surgery.

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