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The dos and don'ts presented in a clinical scenario

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Madalina Anca Lazar*, Ovidiu Muresan**, Calin Rares Roman*, Delia Dima***, Mihai Stefan Muresan°, Gabriel Armencea*, Ciprian Tomuleasa***, Horatiu Rotaru*

**Department of Implantology and Maxillofacial Surgery, Iuliu Hatieganu University of Medicine and Pharmacy Cluj Napoca, Romania*
***Department of Oral and Maxillofacial Surgery, Iuliu Hatieganu University of Medicine and Pharmacy Cluj Napoca, Romania*
****Department of Hematology, Ion Chiricuta Clinical Research Center, Cluj Napoca, Romania*
°Department of Surgery, Iuliu Hatieganu University of Medicine and Pharmacy Cluj Napoca, Romania

Oral surgery for combined haemophilia A and B. The dos and don'ts presented in a clinical scenario.

BACKGROUND: *Haemophilia A (factor VIII deficiency), B (factor IX deficiency) and C (factor XI deficiency) are common genetic bleeding disorders. Most often they are caused by the absence or defective function of coagulation factors, causing inefficient blood clots.*
CASE REPORT: *The present manuscript describes a rare case of a combined haemophilia A and B patient, who underwent several extractions. The therapy and clinical management is presented, in the view of surgeon as well as haematologist.*
CONCLUSION: *These patients are a serious challenge for the oral surgeons due to an increased number of accidents and complications. Scarce literature covering this topic contributes, as well, to the difficult management. Thus, several principles must be considered when diagnosing and treating haemophilia patients.*

KEY WORDS: Haemophilia, Oral surgery

Background

Patients diagnosed with an inherited blood clothing deficiency are at high risk of developing complications, following oral surgery. A very common genetic bleeding disorder is haemophilia. Both forms, A and B, are caused by mutations located on the tenth chromosome. Naturally, men always express the disease and women are usually asymptomatic carriers. The mutations responsible for haemophilia C are located on the fourth chromosome, exposing both sexes to the same amount of risk of expressing the disease. One third of the haemophilia cases appear as the result of spontaneous mutations, which can take place differently in men and women. The female gender is more predisposed to a spontaneous mutation after pregnancy, in the second and third decade of life, while men may go through this event after the fifth decade. In more than half of the cases, acquired haemophilia is combined with other immune disorders, as Sjogren syndrome or systemic lupus erythematosus [1-3].

Eighty percents of haemophilic patients lack the coagulation factor VIII being diagnosed with haemophilia A. Twelve percents lack factor IX, haemophilia B, whereas 8 % lack factor XI, haemophilia C.

Combined congenital deficiencies of clotting factors are recessive and X-linked transmitted, as such they are very rare in women an even scarcer in men. As rare as the congenital defects, *de novo* mutations and large DNA

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Correspondence to: Ciprian Tomuleasa, MD Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy; Department of Hematology, Ion Chiricuta Clinical Research Center, Cluj Napoca, Romania (e-mail: ciprian.tomuleasa@umfcluj.ro)

ABBREVIATION

FEIBA: activated prothrombin complex concentrates

Novoseven®: recombinant factor VIIa

deletions that involve both *factor VIII* and *IX* genes may lead to the expression of both haemophilia A and B [4]
The severity of clinical manifestations is directly correlated with the clotting factor deficiency and it is depicted by various haemorrhagic episode, at different anatomical regions. Hemarthrosis is the most common clinical symptom, affecting any joint, including the temporomandibular joint. One of the most severe manifestation of haemophilia is bleeding in the respiratory tract, that may lead to asphyxia [5].
The normal concentration of clotting factors in haemophiliacs is up to 50% of the average value, while the minimum level required for haemostasis is 12%. In moderate haemophilia, the plasmatic concentration of clotting factors is between 1 and 5%, whereas in severe cases is less than 1% and in mild ones is above 6% [6,7].
By receiving multiple transfusions, patients with severe haemophilia can develop antibodies against the clotting factors VIII or IX. This affects 10% to 25% of haemophilia A patients and 3% of those with haemophilia B. Although bleeding episodes rarely repeat, they are difficult to control and may not respond properly to treatment and prophylaxis [8].
To successfully control the bleeding during and after oral surgery for these patients, a close cooperation between surgeons and haematologists is needed. The treatment protocol available so far consists of local haemostatic measures and systemic treatment with clotting factor concentrates, desmopressin and antifibrinolytic agents. This protocol has reduced the number of bleeding complications after oral surgery in haemophilia patients [9].
In the current manuscript, we present a case of an underdiagnosed patient suffering from combined haemophilia A and B who underwent oral surgery and suffered major complications.

Case Report

A 30-year-old Caucasian man was referred to the Department of Oral and Maxillofacial Surgery – Emergency Clinical Hospital, Cluj-Napoca, Romania, for dental extractions. A written informed consent was signed by the patient before any medical procedure was carried out, a consent that allowed the medical treatment, as well as the presentation and publication of the case report. The medical history of the patient presented severe haemophilia A manifested through haemorrhagic episodes determined by minimal trauma during childhood, a spontaneous abdominal bleeding five years before and an intraparenchymal pulmonary haemorrhage three years before. The last two incidents were treated with plasma and VIII factor concentrate.
After taking the mandibular arch impression, a compressive splint was manufactured in the dental laboratory. Earlier on the day of surgery, the patient was transferred to the haematology department where he received 1000 U.I. of VIII factor concentrate. After having received bilateral inferior alveolar nerve block using articaine (1/100.000) the extraction of teeth 4.7, 4.6, 3.5., 3.6, 3.7, 3.8 were performed. The dental sockets were examined, and the pathological tissue was eliminated. The horizontal mattress suture was performed using rapid resorbable suture (Surgicryl® 4.0). The wound was covered with compressive gauze and the mandibular splint. Four hours following dental surgery, the patient presented moderate bleeding in the pterygomandibular space, associated with acute pain, light swelling of the masseteric region and ecchymosis at the needle insertion. He received another 2x1000 U.I. factor VIII concentrate and compressive gauze, followed by mentocephalic sling. Twenty-four hours later, the patient presented with large intraoral ecchymosis (bilateral on buccal and labial region and the left soft palate), widely spread right laterocervical haematoma and reduced left laterocervical swelling. Due to the large haematoma that could have evolved clinically with asphyxia, an emergency temporary tracheostomy was performed, and a nasogastric tube was placed, as shown in Fig. 1.

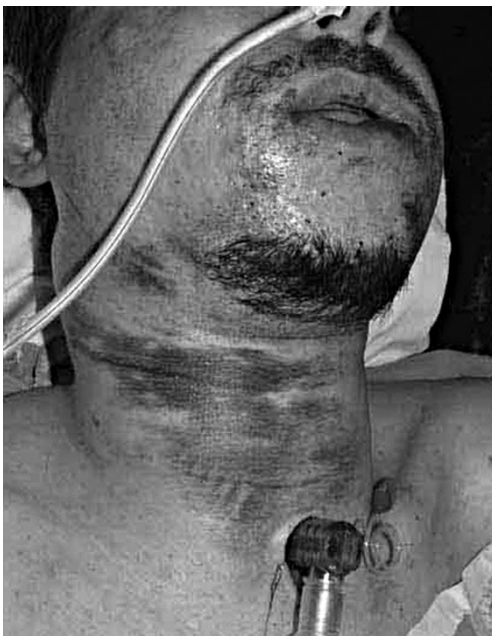

Fig. 1: Widely spread haematoma leading to air compromise and requiring emergency tracheostomy.

Despite systemic treatment with 2500 U.I. factor VIII concentrate, tranexamic acid (3x 0,5g/5ml), 500 mg. hydrocortisone hemisuccinate, blood transfusion (2 units x450 ml) and fresh frozen-plasma (1 unit- 464 ml), the patient general status continued to deteriorate. After 2 more hours, he presented with bilateral palpebral haematoma, intraoral haematomas on the buccal mucosa, bilateral haematoma on the labial area, soft palate and oropharynx that tensioned the soft tissue on the inferior labial region and the posterior part of right sternocleidomastoid muscle. The patient also had bleeding around the tracheostomy tube. On day 4 after the surgical intervention, the patient experienced an episode of psychomotor agitation, tonico-clonic seizures, hypercapnia and discontinuous diuresis. Following the seizures episode, the patient had loss of visual acuity on the next day. Any optic pathway damage was excluded after an ophthalmology consultation. The visual acuity gradually returned to normal within 2 days. The decreased level of hemoglobin (4,7 g/dl) imposed transfusions with fresh frozen plasma (2 units) and erythrocyte mass (1 unit), along with factor VIII concentrate (2500 U.I.). After clinical management, the patient's laboratory tests improved partially, the haemoglobin level being 8,8 g/dl. Despite the treatment, the aPTT (activated partial thromboplastin time) remained high (>120 seconds), patient being readmitted to the haematology department to find out the cause of his bleeding disorder and to manage it properly. He was administered 2000 U.I./day factor VIII concentrate and fresh frozen plasma (2 units/day). Despite therapy, he developed a right ankle haemarthrosis. Laboratory tests were repeated and showed that levels of both clotting factors VIII and IX were less than 1%. Systemic treatment was changed as according to these new findings. The patient received 2.000 U.I. factor VIII, 2500 U.I. factor IX and 2 units of fresh frozen plasma/ day. Consequently, the patient recovered gradually within 5 days.

Discussions

The most important aspect in the dental management of patients with inherited bleeding disorders is the close cooperation between haematologists and oral surgeons. This provides a prophylactic treatment, aiming to reduce bleeding during oral interventions and to help the clot formation [1,9]. As presented in the case report, the main issue was the undiagnosed hemophilia B, which led to inappropriate systemic treatment. A correct diagnosis is essential to ensure the appropriate therapeutic scheme to a patient with bleeding disorders as they may have very similar symptoms. Proper diagnosis can only be made with the support of a comprehensive and accurate laboratory service. Pre-operative factor assay should have been performed to confirm the original diagnosis and to measure pre- and post-infusion clotting factor level. Lower than expected recovery and/or reduced half-life of infused clotting factor may be an early indicator of improper laboratory analyses [10]. This complication affects 10 to 25% of patients with severe haemophilia A and 2 to 3% of patients with haemophilia B. The treatment in the case presented was based on activated prothrombin complex concentrates (FEIBA) and recombinant factor VIIa. FEIBA activates factor X by bypassing the intrinsic pathway, which is dependent on factor VIII. Novoseven® (recombinant factor VIIa) directly actives factor VIII. The chances of success for the treatment with these products are reduced by the uncertainty of the haemostatic effect, the restrains in determining the adequate dosage and the lack of a test to determine the dosage capacity [2,11]. The time interval in which the concentrate prevails in aiding the formation and maintenance of the blood cloth is 10 hours [12,13], before being transferred again to the surgical department.

Depending on the factor activity, systemic therapy consists of intravenous administration of factor VIII/ IX, either prophylactically or at the time of injury. Dose calculations are directed toward achieving a factor VIII activity level of 30-40% for mild hemorrhages, of at least 50% for severe bleeds (as is the case of trauma patients) or prophylaxis of major dental/ general surgeries, and 80-100% in life-threatening hemorrhage.

Besides substitutes of coagulation factors, antifibrinolytic agents should be used. Tranexamic acid inhibits activation of plasminogen to plasmin and promotes the clot stability. Antifibrinolytic treatment with tranexamic acid is usually administered orally three to four times a day, or by intravenous infusion two to three times a day. Tranexamic acid should be prescribed for seven days following dental extractions in patients with intrinsic bleeding disorders [10].

Patients with mild to moderate haemophilia A can be treated with dihydro-D-arginine vasopressin, which increases level of factor VIII [1]. For dental surgery, local anesthesia is one of the most critical steps. Although there are no restrictions to the type of substance used, the anesthetic solution containing vasoconstrictors (such as Articaine®) may provide additional local hemostasis. The mandibular molars are usually treated using the inferior alveolar nerve block. In these special conditions, this block should only be considered after raising the plasmatic level of the clotting factor by up to 50%, as there is a major risk of bleeding into the soft tissue penetrated by the needle. The intraligamentary or interosseous technique should be considered instead of the mandibular block. A lingual infiltration also requires appropriate factor replacement since it is an injection into an area with rich vascularization and no bony surface to guide the needle, raising the risk of asphyxia caused by compression of the soft tissue enlarged by the internal hemorrhage [14].

For our patient, the second misdirection was the dose calculation. Even if the patient had had only hemophilia A, a preoperative dose of 1000 U.I. factor VIII would

have been insufficient to cover the request for multiple dental extraction. Using the consecrated formula (factor VIII dose (U.I.) = G (Kg) x factor VIII required level (% of normal) x 0,5 U.I./kg) a 1500-2000 U.I. factor dose would have been more indicated to obtain a 50% level of activity for factor VIII [11].

Local hemostatic measures are compulsory following dental extraction in hemophilic patients. Classic methods are sutures, collagen veils, oxycellulose, gelatin, fibrin glue and cyanoacrylate [6,15]. To avoid late bleeding caused by suture removal, resorbable materials should be used. Non-steroidal anti-inflammatory drugs and aspirin may favor hemorrhagic complications and should be avoided. Instead, paracetamol can be used as a safe alternative to prevent postoperative pain [13]. In addition, the use of antifibrinolytic agents in intermittent compression can control local bleeding after oral surgery better than the oral splint, giving the disadvantages of this device [2,9]. Some of the main drawbacks of the splint are mucosal injuries, instability which leads to suction effect, giving access to saliva with fibrinolytic activity on the wound surface, and the maceration effect beneath the splint, which stimulates bacterial colonization, leading, in turn, to infection and haemorrhage caused by de streptokinase secreted by the bacteria [2].

For unresponsive bleeding, comprehensive laboratory test should be done without delay. In the described clinical case, this would have probably avoided most of the complications. The hospitalisation time (more than 20 days) and the overall cost of the treatment would have been dramatically reduced if proper diagnosis and prophylaxis have been considered, from the very beginning.

Regarding the usage of local hemostatic methods by means of alveolar plugs, we come to explain the theory behind our surgical act. Giving the expectation of post operatory hemorrhagic complications, involving local and locoregional territories, we found it suitable to use sutures and surgical stent [16-18]. Rather than alveolar meshes, which might have resorbed rather fast in the given condition, even cause other complications on such an abnormal general status. As we described in the article, the local complications were not of great concern, as were the regional ones which threatened by the massiveness of the hematoma, to obstruct the airways. Even if the alveolar plugs would have been proven efficient in preventing the local hemorrhagic complications, the hematoma evolving near the extraction situs would have not been controlled by our alveolar hemostatic attempts. The conclusion that other studies came to, regarding the use of a particular alveolar plug, the oxidized cellulose mesh or fibrin glue. It resumes by affirming that the fibrin glue should not normally be used in patients who have never received human-derived blood products or those who are receiving treatment with recombinant factor VIII or IX because of the potential risks of human viral transmission [19]. So, the best option would have been the oxidized cellulose mesh.

If the replacement therapy is done properly, inferior alveolar nerve block may be used without the risk of bleeding into the muscles along with potential airway compromise due to a hematoma in the retromolar or pterygoid space [20]. The use of local anesthesia was preferred over the general one, considering the potential life-threatening obstruction of the airways caused by the submucosal hemorrhage due to accidents in the intubation sequence. Nasal intubation may lead to hemorrhagic accidents which in turn can lead to aspiration [21]. The local anesthesia offers a relative control over hemostasis through its vasoconstrictor content. Another option would have been intravenous anesthesia, but it was not considered in our particular case due to the extent of the surgery needed.

Conclusion

It is crucial to identify patients with bleeding disorders before performing dental extractions. Managing these patients requires a close cooperation between haematologists and oral surgeons. As such, a strict prophylactic protocol to diminish postsurgical bleeding, which comprises of coagulation factors administration and local haemostasis techniques, is required.

By describing this clinical scenario, we emphasize the importance of following strict steps when managing patients with bleeding disorders. Even if combined haemophilia is a very rare entity, all the laboratory tests must be carried out and a correct diagnostic must be established from the beginning, to avoid prolonged and unresponsive bleeding to systemic and local measures.

Riassunto

Le emofilia A (carenza di fattore VIII), B (carenza di fattore IX) e C (carenza di fattore XI) sono comuni patologie dell'emogoagulazione su basi genetichei. La carenza funzionale o l'assenza di fattori della coagulazione sono causa della formazione di coaguli ematici inefficienti.

Viene presentato qui il caso raro di un paziente affetto da emofilia A e B, sottoposto a più estrazioni dentarie, e vengono illustrati il trattamento e la gestione clinica da parte del chirurgo e dell'ematologo.

Questi pazienti rappresentano una seria sfida per i chirurghi orali a causa di un aumento del numero di incidenti e complicanze. La scarsa letteratura che copre questo argomento contribuisce anche alla difficile gestione. Pertanto, durante la diagnosi e il trattamento dei pazienti affetti da emofilia devono essere presi in considerazione diversi principi.

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References

1. Abramowicz S, Staba SL, Dolwick MF, Chen DR: *Orthognathic surgery in a patient with hemophilia A: report of a case*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008; 105(4):437-39.

2. Frachon X, Pommereuil M, Berthier AM, et al.: *Management options for dental extraction in hemophiliacs: A study of 55 extractions (2000-2002).* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2005; 99(3):270-75.

3. Heiland M, Weber M, Schmelzle R: *Life-threatening bleeding after dental extraction in a hemophilia A patient with inhibitors to factor VIII: A case report*. J Oral Maxillofac Surg, 2003; 61(11):1350-353.

4. Shetty S, Ghosh K, Parekh S, Mohanty D: *Combined factor VIII and IX deficiency in a family.* International Journal of Laboratory Hematology, 2001; 23(3):201-4.

5. Gómez-Moreno G, Cutando-Soriano A, Arana C, Scully C: *Hereditary blood coagulation disorders: Management and dental treatment*. J Dent Res, 2005; 84(11):978-85.

6. Gómez-Moreno G, Cañete-Sánchez ME, Guardia J, Castillo-Naveros T, Calvo-Guirado JL: *Orthodontic management in patients with haemophilia. About two clinical cases*. Haemophilia, 2010; 1:3.

7. Peisker A, Raschke GF, Schultze-Mosgau S: *Management of dental extraction in patients with Haemophilia A and B: A report of 58 extractions.* Medicina oral, patologia oral y cirugia bucal, 2014; 19(1):e55.

8. Brewer AK, Roebuck EM, Donachie M, et al.: *The dental management of adult patients with haemophilia and other congenital bleeding disorders*. Haemophilia, 2003; 9(6):673-77.

9. Franchini M, Rossetti G, Tagliaferri A, et al: *Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers*. Haemophilia, 2005; 11(5):504-09.

10. Srivastava A, Brewer AK, Mauser Bunschoten EP, et al.: *Guidelines for the management of hemophilia*. Haemophilia, 2013; 19(1).

11. Brewer A, Correa ME: *Guidelines for dental treatment of patients with inherited bleeding disorders.* Haemophilia, 2005; 11:504-09.

12. van Galen KP, Engelen ET, Mauser-Bunschoten EP, van Es RJ, Schutgens RE: *Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions.* Cochrane Database Syst Rev, 2015; (12):CD011385.

13. Peisker A, Raschke GF, Schultze-Mosgau S: *Management of dental extraction in patients with Haemophilia A and B: a report of 58 extractions.* Med Oral Patol Oral Cir Bucal, 2014; 19(1):e55-60.

14. Shastry SP, Kaul R, Baroudi K, Umar D: *Hemophilia A: Dental considerations and management.* J Int Soc Prev Community Dent, 2014; 4(Suppl 3):S147-52.

15. Piot B, Sigaud-Fiks M, Huet P, Fressinaud E, Trossaërt M, Mercier J: *Management of dental extractions in patients with bleeding disorders*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2002; 93(3):247-50.

16. Israels S, Schwetz N, Boyar R, McNicol A.: *Bleeding disorders: characterization, dental considerations and management*. J Can Dent Assoc, 2006; 72(9):827.

17. Watterson C, Beacher N: *Preventing perioperative bleeding in patients with inherited bleeding disorders*. Evid Based Dent, 2017; 18(1):28-29.

18. Berce C, Muresan MS, Soritau O, Petrushev B, Tefas L, Rigo I, Ungureanu G, Catoi C, Irimie A, Tomuleasa C: *Cutaneous wound healing using polymeric surgical dressings based on chitosan, sodium hyaluronate and resveratrol. A preclinical experimental study*. Colloids Surf B Biointerfaces, 2018; 163:155-66.

19. Khokhar RS, Hussain A, Khan MU, Hajnour M, Qureshi S, Aqil M: *Nsthetic management of patient with hemophilia a undergoing emergency ventriculoperitonealshunting: A case report and review of literature.* Saudi J Anaesth. 2016;10(4):474-476.

20. Shastry SP, Kaul R, Baroudi K, Umar D: *Hemophilia A: Dental considerations and management.* J Int Soc Prev Community Dent, 2014; 4(Suppl 3):S147-52.

21. Mistry T, Dogra N, Chauhan K, Shahani J: *Perioperative Considerations in a Patient with Hemophilia A: A case report and review of literature*. Anesth Essays Res, 2017; 11(1):243-45.