

Transfusion of fibrinogen concentrate before dental extractions in patients with afibrinogenemia: a narrative review supported by a case report with a proposed treatment protocol

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Afibrinogenemia is a coagulation disorder that occurs with a frequency of 1-2 cases/1,000,000 population and is characterized by a lack of capacity to synthesize fibrinogen. The predominant symptoms related to fibrinogen deficiency are mucocutaneous bleeding, bleeding from the gastrointestinal tract, genital tract or other vascularized tissues as well as excessive bleeding after minor injuries or accidental cuts. Thromboembolic complications and impaired wound healing may also occur. Due to the rarity of the disease, there are no recommendations about fibrinogen substitution before dental procedures (including dental surgery). The purpose of this review is to discuss the indications for the transfusion of a coagulation factor in the preparation of a patient with afibrinogenemia for dental extraction. The article is a narrative review with a proposed management protocol for the dental procedure. The authors have included information from previously published case reports, research studies, and review papers as well as their own case report.

Keywords: afibrinogenemia, hemorrhage, hemorrhagic disorders, hemostasis, tooth extraction.

INTRODUCTION

Congenital afibrinogenemia is a rare coagulation disorder characterized by the inability to synthesize fibrinogen and is the most severe form of fibrinogen deficiency^{1,2}. Afibrinogenemia occurs with a frequency of 1-2 cases/1,000,000 population³. According to the database maintained by the Institute of Hematology and Blood Transfusion in Warsaw, 116 patients with fibrinogen deficiency (afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia) were reported in Poland in 2018⁴. The diagnosis of afibrinogenemia is made by demonstrating the absence of fibrinogen (clotting factor I) in plasma⁵⁻⁷. The activity of other clotting factors remains normal⁸. The differential diagnosis includes congenital deficiencies of other clotting factors and acquired fibrinogen deficiency. The treatment of choice is replacement therapy with fibrinogen concentrate with the aim of maintaining fibrinogen levels in the plasma above 50 mg/dL, depending on different clinical situations. Previously, before the possibility of using clotting factor concentrates,

fresh-frozen plasma and cryoprecipitate could be administered, but this practice was abandoned because of the risk of blood-borne transmission of viruses⁸⁻¹⁰. For surgical procedures, the target fibrinogen concentration is approximately 100 mg/dL, or 150 mg/dL for pregnant women. No recommendations on the preparation of patients with afibrinogenemia for dental treatment, including dental surgery, have been established. The fibrinogen level in the treatment of bleeding patients is likely to depend on the clinical situation¹¹.

MATERIAL AND METHODS

Strategies and selection of the search criteria

A literature review was performed, including case reports, guidelines/recommendations, scientific studies, and review papers on the pathogenesis, diagnosis, treatment, and dental management of patients with afibrinogenemia or hemophilia, and fibrinogen concentrate. Due to the limited number of original articles and the lack of randomized or quasi-randomized trials published before the date of completion of the search process, as recommended by the Cochrane Methodology Review Groups, this review is narrative in nature. Special attention was paid to the risk of bleeding during dental extraction of patients with hemophilia and the possible need for transfusion of a deficient coagulation factor. Articles were included in the appraisal if the subject area overlapped with the topic under study and if there was sufficient evidence. The PubMed/Medline database was used to obtain information from the National Library of Medicine. Two search strategies were used: the first was based on text word searches and the second used Medical Subject Headings (MeSH). Articles were analyzed regardless of original language, date, and publication status. Due to the rarity of afibrinogenemia and the small number of scientific studies, we included our own case report. The examination and treatment of the patient described were performed in accordance with ethical principles within the scope of cooperation between the Department of Hematology and Bone Marrow Transplantation of Poznan University of Medical Sciences, the Department of Conservative Dentistry and Endodontics of Poznan University of Medical Sciences and the Dental Surgery Clinic of the University Center of Dentistry and Specialized Medicine in Poznan. The aim of

the study was to compile information on afibrinogenemia and to share our experience.

RESULTS

This review highlights the need for intravenous administration of fibrinogen concentrate prior to dental surgery in a patient with afibrinogenemia.

Extraction of a lower wisdom tooth with mesio-angular retention in a patient with afibrinogenemia

A 27-year-old woman with congenital afibrinogenemia was referred to the Dental Surgery Clinic at the University Center of Dentistry and Specialist Medicine in Poznan for the extraction of tooth 38. The patient had been treated for afibrinogenemia from early childhood. The indication for extraction was deep caries and incorrect positioning of the tooth in the dental arch: medial-angular retention prevented effective oral hygiene in the area of teeth 37 and 38 which led to caries on the distal surface of tooth 37.

During the patient's consultation at the Department of Conservative Dentistry and Endodontics, Poznań University of Medical Sciences, orthopantomography was performed (**Figure 1**), oral hygiene status was assessed using the simplified Oral Hygiene Index¹² and the Approximal Plaque Index¹³, and gingival status was evaluated using a test of bleeding on probing¹⁴. The orthopantomograph showed the presence of various cavities in teeth 15, 26, 37, 38, 45, and 46. The patient was advised of the need for conservative treatment. Based on the clinical and radiological examinations the patient was referred for endodontic treatment of tooth 15.

Bleeding on probing¹⁴ is an index based on the dichotomous parameter of the presence or absence of bleeding when probing a gingival pocket. This dental index in the patient was 93.75%. The simplified Oral Hygiene Index¹² was assessed for six teeth, teeth 16, 21, 24, 36, 41, and 44. The debris index with a value of 0 and the calculus index with a value of 1/3 were evaluated separately. The effectiveness of interdental hygiene treatments was evaluated using the Approximal Plaque Index¹³. In quadrants 1 and 3, the interdental spaces on the side of the oral cavity proper were evaluated, and in quadrants 2 and 4, the interdental spaces on the side of the oral vestibule were evaluated. The result of 37.5% indicated good oral hygiene.

In her medical history, the patient reported intramuscular/joint bleeding, prolonged bleeding from minor cuts or after



Figure 1 - Orthopantomograph taken before extraction of tooth 38

trauma, a tendency to bruise easily, gingival bleeding, heavy/long menstrual bleeding and gastrointestinal bleeding. According to subjective assessment, the patient's oral health was described as good. In her dental history, the patient reported that she brushes her teeth for about half a minute, twice a day, with a manual toothbrush. The patient flosses, does not use mouthwash, does not clean her tongue and visits the dentist regularly every 6 months. The patient was prepared for the tooth extraction procedure at the Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences. Regular fibrinogen testing over the past 2 years documented fibrinogen levels <35 mg/dL (reference values 200-439 mg/dL, quantitative determination of fibrinogen using the Clauss method, detection limits of the test 35-1,000 mg/dL). The patient was given 3 g of fibrinogen concentrate (Riastap [CSL Behring, Marburg, Germany])¹⁵ intravenously before the procedure. Additionally, in the case of bleeding, postoperative administration of 1 g of fibrinogen concentrate was recommended. Oral tranexamic acid (Exacyl [Cheplapharm Arzneimittel, Greifswald, Germany]) at a dose of 3×1 g/day before surgery, on the day of surgery and for 5 consecutive days

was also recommended. The patient was instructed to avoid the use of drugs that impair hemostasis, including non-steroidal anti-inflammatory drugs, before and after the procedure.

Before the tooth extraction the patient was given infiltration anesthesia and an inferior alveolar nerve block was performed with articaine and adrenaline. The roots were separated with a dental handpiece cooled with 0.9% NaCl. Excessive bleeding occurred during the procedure making it difficult to see the area of surgery. After extraction, a hemostatic dressing made of purified porcine gelatin foam (Spongostan [Ethicon, Bridgewater, NJ, USA]) was applied and the margins were tightly sutured with single knotted stitches using 5.0 surgical sutures. The patient was instructed to have the sutures removed at the Dental Surgery Clinic 7 days after the procedure. It was recommended that she use paracetamol, paracetamol with codeine (Dafalgan Codeine [UPSA, Agen, France]) or paracetamol with tramadol (Zaldiar [Grünenthal Pharma, Aachen, Germany]) to alleviate any pain. The patient was instructed to clamp a compression tampon for 1 hour after the procedure and was also advised to take amoxicillin with clavulanic acid (875 mg + 125 mg one tablet, twice

daily for 7 days). Due to excessive bleeding during the procedure, the patient was referred to the Department of Hematology and Bone Marrow Transplantation, where her plasma fibrinogen level was checked (50 mg/dL) and an additional 2 g of fibrinogen concentrate were administered intravenously. The patient's detailed laboratory results are shown in **Table I**. An additional 1 g of fibrinogen concentrate was given on day +1 to +3 and also on the day of suture removal after surgery. The patient did not complain of late bleeding.

DISCUSSION

Clinical picture of afibrinogenemia

The clinical picture of afibrinogenemia correlates with the level of fibrinogen activity. The severity of bleeding can vary from mild to life-threatening^{5,16-18}. Patients with afibrinogenemia may present with petechiae, bleeding from the umbilical cord stump, nose, gums, gastrointestinal tract, genital tract, and urinary tract, bleeding into muscles or with intraperitoneal bleeding^{3,16}. Moreover, intracranial hemorrhages¹⁹, spontaneous rupture of the spleen^{1,20}, bone cysts¹ and, in women, menstrual bleeding²¹, spontaneous abortions and pre- or postpartum bleeding have been reported^{5,15,22-24}. Asymptomatic periods may occur between bleeds⁵. Abnormal bleeding is usually observed as early as the

neonatal period; in 85% of cases bleeding from the umbilical cord stump draws attention^{5,17,23-25}. Patients with afibrinogenemia experience excessive bleeding after minor trauma or surgery^{21,26}. In addition, delayed and abnormal wound healing^{3,23}, as well as arterial and venous thromboembolic complications related or unrelated to additional risk factors, have been reported in the literature^{1,9,23,24,27-31}.

Dental treatment of patients with congenital afibrinogenemia

Because of the rarity of congenital fibrinogen deficiency, physicians and dentists lack experience in managing patients with afibrinogenemia. The dental treatment of patients with this disorder has rarely been described in the literature and thus there are not sufficient studies to create strictly defined guidelines. The best known congenital hemorrhagic disorders to date are hemophilia and von Willebrand disease²¹. In our opinion, in the case of dental treatment of patients with congenital afibrinogenemia, it is worth applying principles similar to those for people with hemophilia and to support the recommendations of international and national organizations working for the benefit of patients with bleeding disorders, such as the European Haemophilia Consortium³² and the World Federation of Hemophilia (WFH)³³. It should

Table I - Laboratory findings before and after extraction of a lower wisdom tooth

	Three months before surgery	Day of treatment after 3 g of fibrinogen concentrate	Five days after surgery before iv fibrinogen concentrate*	Seven days after surgery (+ 1 hour after Riastap)
Fibrinogen	<35 mg/dL	50 mg/dL	36 mg/dL	64 mg/dL; (156 mg/dL)
PT	>320 s		>320 s	15.1 s (14.4 s)
PT (1+1)	11.9 s		12.6 s	12.4 s correction
TT	>300 s		>300 s	24.5 s (19.2 s)
TT (1+1)	18.3 s		17.7 s	17.4 s correction;
Clotting time in FIBTEM		84 s	103 s	70 s (56 s)
Maximum clot firmness in FIBTEM		5 mm	6 mm	8 mm (12 mm)
C-reactive protein	<4 mg/dL		6 mg/dL	<4 mg/dL
Red cell count	5.33×10 ¹² /L		4.94×10 ¹² /L	4.85×10 ¹² /L
White blood cell count	8.24×10 ⁹ /L		10.39×10 ⁹ /L	8.87×10 ⁹ /L
Platelet count	318×10 ⁹ /L		384×10 ⁹ /L	398×10 ⁹ /L
Hemoglobin	8.5 mmol/L		8.5 mmol/L	8.4 mmol/L
Hematocrit	0.43		0.41	0.40

*Note that values in this column are the result of administration of fibrinogen 3 g before surgery, plus 2 g after surgery, plus 1 g on day +1 and 1 g on day +3. PT: prothrombin time; TT: thrombin time; FIBTEM: fibrinogen part of rotational thromboelastometry (ROTEM).

be remembered that the prevention of bleeding in afibrinogenemia requires measures such as the avoidance of actions with a high risk of bleeding and the selection of procedures with the lowest risk of bleeding. Moreover, it is necessary to consider hematologists' treatment plans with specialists in other fields³⁴.

The Dental Committee of the WFH³⁵ confirmed that supplementation of a deficient coagulation factor in a patient with a congenital bleeding disorder may be necessary, among other things, before tooth extraction³⁶ or before inferior alveolar nerve block and infiltration anesthesia administered from the side of the oral cavity proper³⁷. For hemophilia A, factor VIII levels of at least 50% must be achieved prior to administration of anesthesia; the factor half-life is 12 hours³⁵. For afibrinogenemia, the target fibrinogen concentration before surgery is approximately 100 mg/dL³. There are no specific guidelines on fibrinogen levels for specific surgical procedures, nor are there recommendations on optimal fibrinogen concentrations during dental procedures or fibrinogen concentrate pharmacokinetics. The half-life of fibrinogen is 3 to 5 days, which raises questions about the necessity of administering fibrinogen, cryoprecipitate or fresh-frozen plasma after surgery. In our opinion, the decision to administer fibrinogen after a dental extraction procedure should be made on an individual basis. As the source of the clotting factor to be administered, preference should be given to using specific concentrates of recombinant or virally inactivated plasma-derived coagulation factors (if available) rather than fresh-frozen plasma or cryoprecipitate³⁴. In the patient described here, it was decided to reintroduce fibrinogen after surgery due to excessive bleeding during the procedure and the course of the dental extraction. The WFH also recommends using protocols that include local hemostatic strategies³⁸, such as stitching, fibrin glues, oxidized cellulose (for example, Surgicel [Eticon]) and fibrinolytic agents (tranexamic acid) before the procedure³⁵. It should be remembered, however, that tranexamic acid may be contraindicated in the presence of a high risk of thrombosis³⁴. In addition, tranexamic acid is not licensed for use in children, so care should be taken when using it in neonates³⁴.

Only a few tooth extraction procedures in patients with afibrinogenemia have been described in the literature. One of the described procedures was performed under

general anesthesia and involved partially retained wisdom teeth in the mandible. In this case, the patient received cryoprecipitate approximately 1 hour before surgery, and perioperative bleeding was estimated to be minimal. Despite the lack of re-administration of a fibrinogen-containing preparation after the procedure, no postoperative complications occurred and the wounds healed properly³⁹. Another reported case involved the incision of an odontogenic abscess and deferred extraction of the causative teeth. The abscess was incised in an outpatient setting after administration of fibrinogen concentrate. Abnormal bleeding did not occur. The next step was a deferred multiple tooth extraction. The patient was given fibrinogen concentrate before and after the procedure. The decision to re-administer fibrinogen was based on laboratory tests. On postoperative day 8, no delayed healing or abnormal bleeding was observed²⁵. These cases prove that dental extractions in patients with afibrinogenemia can be performed in an outpatient setting. During the preparation for surgery, the risk of bleeding should be taken into account as well as the possibility of thromboembolic complications (such complications do not occur in other congenital bleeding disorders). Given the symptoms of afibrinogenemia and the possibility of complications³⁹, good cooperation between the hematologist and the dentist, along with a thorough examination of the patient, are prerequisites for dental surgery. According to the literature, periods without symptoms of the clotting disorder may be longer in the case of afibrinogenemia than in the case of hemophilia³; nevertheless, the Bleeding on Probing Index in the case of the patient described in this article had a value close to 100%.

Accidental damage to the mucosa, for example by using a rubber dam, should be avoided in all dental procedures^{35,37}. It is extremely important to maintain a healthy periodontium in order to prevent premature tooth loss and minimize bleeding³⁵. High-risk procedures are those in the field of periodontal surgery, which should be considered only in the case of good oral hygiene and a lack of effectiveness of conservative treatment³⁵. There are no contraindications to prosthetic and orthodontic treatment³⁵.

Due to the difficulties in treating patients with coagulation disorders, the WFH pays special attention

Table II - Suggestions for the preparation of a patient with afibrinogenemia for extraction of an impacted wisdom tooth, and treatment during and after the procedure as well as postoperative recommendations

Patient evaluation	Medical interview	Bleeding phenotype/incidence of bleeding
		Previous surgical procedures
		Symptoms of bleeding disorder
		Treatments for bleeding disorder
	Laboratory tests	PT, APTT, TT, fibrinogen, FIBTEM
Radiological examination	Intraoral X-ray	
	Or pantomographic X-ray	
	Or cone-beam computed tomography	
Clinical examination	Dental indices, for example bleeding on probing, approximal plaque index, oral hygiene index or the simplified oral hygiene index	
Management before surgery on the day of procedure	Intravenous fibrinogen concentrate	<p>A palma fibrinogen level >100 mg/dL (1 g/L) is usually sufficient to treat or prevent spontaneous or surgical bleeding In the case of severe hemorrhage during the procedure, it is suggested that a fibrinogen level of >150 mg/dL (1.5 g/L) is achieved. The expected recovery for fibrinogen is 0.017 g/L per mg/kg</p> <p>Recommended pharmacological treatment Dose of fibrinogen concentrate (human) (mg/kg of body weight)¹⁵</p> $= \frac{([Target\ level\ (mg/dL) - measured\ level\ (mg/dL)]}{(1.7\ (mg/dL\ per\ mg/kg\ body\ weight))}$ <p>and dose adjusted after assessment of thrombotic risk 1 g vials</p> <p>Plasma half-life of fibrinogen 3-4 days</p> <p>The calculated dose for our patient (65 kg body weight) was 3-4 g of fibrinogen concentrate Treatment, 1 hour prior to surgery, for patients with afibrinogenemia weighing approximately 70 kg is 3 g of intravenous fibrinogen concentrate</p>
	Tranexamic acid - orally	The standard dose is 25 mg/kg every 6-8 hours, starting administration 1 day before surgery, then continuing on the day of surgery and for 5 to 7 consecutive days after surgery
Early management after tooth extraction	Hemostatic dressings	e.g. fibrin glues, oxidized cellulose (Surgicel ³⁶), Spongostan, TachoComb ³⁴
	Sutures	Recommended ³⁶
	Intravenous fibrinogen concentrate	Individual decision based on bleeding during procedure In the case of our patient, an additional 1 g of fibrinogen concentrate was given after checking the fibrinogen level on the day of the procedure
Longer-term management after the procedure and postoperative recommendations	Healing control and removal of sutures	Postoperative fibrinogen 1 g intravenously on day +1, +3 days and on the day of suture removal, or consider in the case of any unexpected bleeding complications
	Compression tampon	1 hour
	Painkillers	Avoid the use of drugs that impair hemostasis before and after the procedure, including non-steroidal anti-inflammatory drugs
		Paracetamol / paracetamol with codeine / paracetamol with tramadol
Intravenous fibrinogen concentrate	Individual decision	

PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; FIBTEM: fibrinogen part of rotational thromboelastometry (ROTEM).

to the prevention of oral diseases³⁵. Subjects are recommended to brush their teeth at least twice a day using a toothpaste containing fluoride (1,000 ppm up to 7 years of age, 1,400 ppm over 7 years of age) and a brush with medium-hard bristles; interdental hygiene is also recommended. The aforementioned doses of fluoride in

toothpaste and exogenous fluoride supplementation are not recommended for subjects living in a region in which the level of fluoride in drinking water exceeds 1 ppm. Control visits at the dentist's office should take place at least once every 6 months. The consumption of sugars or acids should be limited to main meals.

Comparative analysis of hemophilia and afibrinogenemia

Hemophilia is a congenital coagulation disorder that occurs more frequently than afibrinogenemia. Hemophilia A is caused by a deficiency of coagulation factor VIII, whereas hemophilia B is caused by a deficiency of coagulation factor IX. Hemophilia and afibrinogenemia differ in their mode of inheritance: hemophilia is inherited in a recessive, sex-linked manner and afibrinogenemia in an autosomal recessive manner. The most common cause of congenital afibrinogenemia is a homozygous mutation of the gene encoding the alpha chain of fibrinogen¹⁶. In the case of hemophilia, almost exclusively men are affected⁴⁰, while afibrinogenemia affects both men and women. Differences are also seen in basic laboratory tests: in hemophilia, the prothrombin time and bleeding time remain normal. The mean annual incidence of bleeding in patients with afibrinogenemia has been shown to be lower than in patients with severe hemophilia⁵. On this basis, it has been concluded that patients with afibrinogenemia have longer asymptomatic periods and less bleeding⁵. Although there are specific symptoms related to afibrinogenemia or hemophilia, some clinical manifestations occur in both diseases, such as bleeding after minor trauma or surgery. In addition, afibrinogenemia may result in impaired wound healing due to fibrinogen abnormalities^{5,16,41}. In both hemophilia and afibrinogenemia, hemorrhagic complications can occur during dental procedures. It is therefore recommended that the deficient coagulation factor is supplemented before surgery, and that appropriate wound care is implemented after the procedure³⁵. Due to the different half-lives of factors I, XIII and IX, there may be differences in the need to administer the deficient clotting factor after a dental procedure. In both hemophilia and afibrinogenemia, it is recommended that accidental damage to the mucous membranes is avoided during all dental procedures and that the procedures performed should be as atraumatic as possible. Spontaneous splenic rupture has been described in patients with afibrinogenemia in literature^{1,5,20}. This complication has not been described in patients with congenital hemophilia. Due to the need for intravenous administration of blood products, patients with congenital bleeding disorders are at increased risk of developing blood-borne viral

infections, such as those caused by hepatitis C virus, hepatitis B virus, human immunodeficiency virus and others^{42,43}. In the case of fibrinogen deficiency, in addition to bleeding, thromboembolic complications have been described^{1,9,23,24,27-30}. In patients with afibrinogenemia, bleeding into the muscles and joints may occur, and hemarthrosis may develop (in approximately 20% of cases). However, in contrast to people with severe hemophilia, patients with afibrinogenemia rarely develop debilitating arthropathy¹⁶.

CONCLUSIONS

On the basis of the case described, the literature review and our own experience, we have formulated suggestions for the preoperative and postoperative management of extraction of an impacted wisdom tooth in a patient with afibrinogenemia (Table II). It should be remembered that decisions should be made according to the risk of bleeding, the conditions of the procedure and thrombotic risk factors. Before oral surgery, a patient with congenital afibrinogenemia must have a consultation with a hematologist. Supplementation of the deficient fibrinogen is essential. In certain cases, the extraction procedure can be performed in an outpatient setting. It is advisable to protect the wound with a hemostatic dressing and sutures. The patient should be given precise instructions for the postoperative period, including avoidance of medications that impair hemostasis (for example, non-steroidal anti-inflammatory drugs). The patient must be monitored after the procedure and undergo scheduled follow-up visits to detect any late bleeding. When in doubt about the dental treatment of patients with afibrinogenemia it is worth reviewing recommendations for other bleeding disorders, including hemophilia.

The Authors declare no conflicts of interest.

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