Hereditary Blood Coagulation Disorders: Management and Dental Treatment

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J DENT RES 2005 84: 978
DOI: 10.1177/154405910508401102

CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

Hereditary Blood Coagulation Disorders: Management and Dental Treatment

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J Dent Res 84(11):978-985, 2005

ABSTRACT

Patients with hereditary hemostatic disorders, characterized by a tendency to bleeding or thrombosis, constitute a serious challenge in the dental practice. Advances in the medical diagnosis of hemostatic disorders have exposed dental professionals to new patients not amenable to the application of the management protocols associated with other, more well-known, disorders. It is the aim of this paper to review the evidence, to highlight the areas of major concern, and to suggest management regimens for patients with hereditary hemostatic disorders. An extensive review has been made (PubMed, Science Direct, Web of Knowledge, etc.) of literature pertaining to hereditary disorders affecting blood coagulation factors and how they affect the practice of dentistry. Several aspects relating to the care of such patients must be recognized and taken into consideration when dental treatment is planned. Replacement of deficient coagulation factors ensures that safe dental treatment will be carried out. However, the half-life of such coagulation factors requires that dental treatment be specifically planned and adapted to the type of pathology involved.

KEY WORDS: hereditary coagulation disorders, dental treatment.

Received December 9, 2004; Accepted June 20, 2005

INTRODUCTION

Hereditary disorders of the coagulation factors involved in blood hemostasis (*i.e.*, both pro- and anticoagulant processes, with tendencies to cause thrombosis and bleeding, respectively) are not well-understood in the dental setting. Most dental professionals focus on aspects such as hemophilia A or B, or Von Willebrand's disease, with little reference to the other factors that also intervene in blood clot formation and destruction—possibly because the processes involved are less commonly seen in dental practice (Scully *et al.*, 2002).

The hematological treatments needed for patients with such hemostatic disorders vary considerably among individuals and even in the same individual at different times in dental management. As a result, dental treatment may require modification according to the hematological process involved, or, alternatively, the dental therapy needed may cause the hematologist to change the treatment strategy (Little *et al.*, 1997; Di Paola *et al.*, 2001). Patients with these defects are in particular need of preventive oral health care, to minimize the need for surgical interventions.

The aims of the present study were to:

- review the hereditary disorders involving the different hemostatic factors;
- examine the different hematological treatments indicated in each disorder; and
- define the aspects which must be taken into account in planned dental treatment for such patients, such as the half-life of the transfused factor, therapeutic measures aimed to increase the levels of a deficient factor, the need for multiple transfusions, and, where necessary, the use of anti-fibrinolytic medication.

We also highlight the importance of identifying patients receiving warfarin for plasma deficiencies, and those at risk for a tendency to thrombosis.

HEMOSTASIS

Several physiological mechanisms keep the blood constantly in a fluid state, to allow for adequate tissue perfusion, while other mechanisms are responsible for generating localized blood clots or thrombi in those situations and locations involving vascular endothelial damage—to prevent blood from 'escaping' from the vascular system. The term "hemostasis" is used in reference to the global mechanisms involved in maintaining internal blood equilibrium, and which function in five sequential phases (François *et al.*, 1989; Deloughery, 1999):

Vasoconstriction

This occurs in the zone where a blood vessel ruptures or damage has occurred. While this first reaction, alone, is unable to stop bleeding, it does reduce blood loss (Fig. 1) (Troy, 1988; Cutando and Gil, 1999).

Platelet Aggregation

The platelets (or thrombocytes) adhere to the sub-endothelial matrix exposed as a consequence of blood vessel wall damage. Platelets

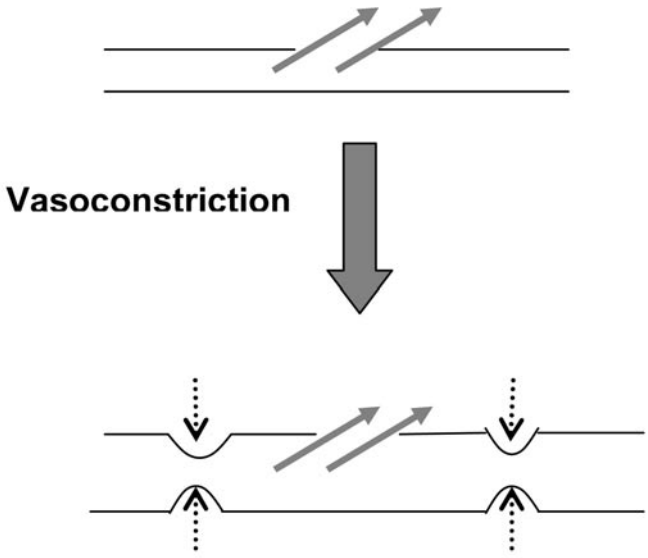

Figure 1. First (vascular) phase of the hemostatic process.

Table 1. Coagulation Factors

Factor	Name
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Calcium
V	Labile factor, pro-accelerin (accelerator globulin)
VI	Not designated
VII	Proconvertin, co-thromboplastin
VIII	Antihemophilic factor; Von Willebrand factor
IX	Plasma thromboplastic component; Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin-stabilizing factor
Fitzgerald F	High-molecular-weight kininogen
Fletcher F	Pre-kallikrein

produce serotonin and thromboxane A2 (TXA2), which, in turn, have three functions: further enhancement of the initiated platelet aggregation process; increased vasoconstriction; and the activation of blood coagulation (clotting) factors (F) X (Stuart-Prower factor) and II (prothrombin) (Rand *et al.*, 2003).

Platelets require the intervention of a plasma protein known as Von Willebrand factor (vWF), which facilitates platelet adhesion to the sub-endothelial matrix of the exposed endothelium. As the different blood-clotting steps progress, hemostatic action intensifies. Platelet disorders cause severe impairment of this second and subsequent hemostatic steps, and hemostasis is ultimately compromised as a result (Fig. 2) (Kehrel, 2003).

Participation of the Coagulation Proteins

The coagulation proteins are plasma proteins (close to 20 in total) synthesized in the liver (Table 1). In fact, this does not represent a true 'third step' of a sequential process; rather, coagulation protein action seeks to achieve the same effects as the fourth hemostatic step, albeit through a different pathway: the formation of thrombin. The coagulation process involves two different pathways: the intrinsic coagulation pathway or cascade, and the much faster extrinsic pathway. Some coagulation proteins characteristically participate in the former cascade, while others are involved in the latter. Both pathways converge to form prothrombin (or factor II) and thrombin (Fig. 3) (Narayanan and Hamasaki, 1998).

The extrinsic coagulation pathway is activated when inactive circulating factor VII (proconvertin) is activated by the presence of a tissue (or hystic) factor released from damaged vascular endothelium. Activated F VII, in turn, activates factors IX ('Christmas factor' or plasma thromboplastic component [PTC]) and X. Activated factor X then causes inactive prothrombin (F II) to convert to the active form (thrombin), which finally facilitates the conversion of fibrinogen into fibrin. In this sense, thrombin is clearly located at the center of the global hemostatic process.

The intrinsic coagulation pathway is initiated by the presence in plasma of so-called plasma contact factors, which attract factor XII (Hageman factor) and pre-kallikrein. In this context, an important role is played by phospholipids, which, in turn, attract F XI (plasma thromboplastin antecedent [PTA]). The latter activates F IX in the required presence of ionic calcium (Ca^{2+}). Factor IX, in turn, activates F X in the presence of factor VIII (antihemophilic factor A), and activated F X then activates F II (prothrombin) in the presence of factor V (accelerator globulin), resulting in the production of thrombin. Once small amounts have been generated, thrombin acts upon factors V and VIII to increase its own production at a much faster rate (positive feedback) (Troy, 1988). Protein C inactivates factors V and VIII (Norris, 2003).

When any of the above-mentioned coagulation factors is defective or deficient, a bleeding tendency results. This is the case, for example, in the hereditary chromosome X-linked coagulation disorders, in which factors VIII and IX are affected. Von Willebrand's disease exhibits an autosomal-dominant or -recessive hereditary pattern, while the rest of the anomalies show an autosomal-recessive hereditary trait.

The most common and therefore important examples of such hereditary coagulation disorders are: (a) hemophilia A (F VIII deficiency); (b) Von Willebrand's disease, characterized

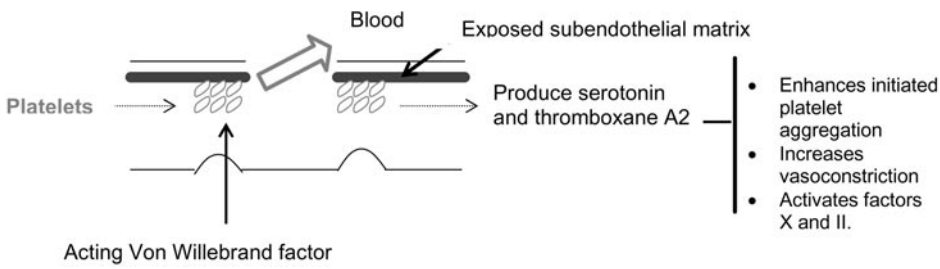

Figure 2. Second (platelet) phase of the hemostatic process.

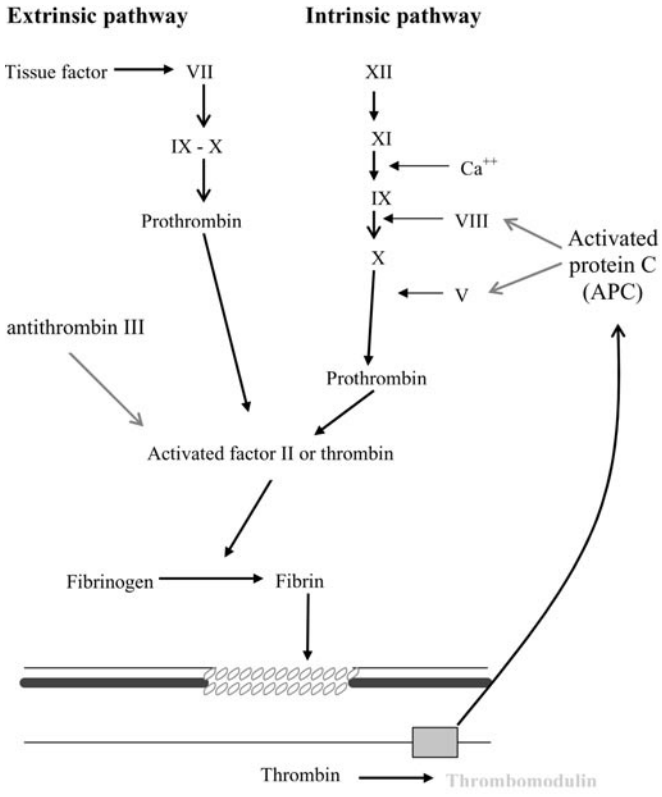

Figure 3. Third and fourth (fibrin) phases of the hemostatic process.

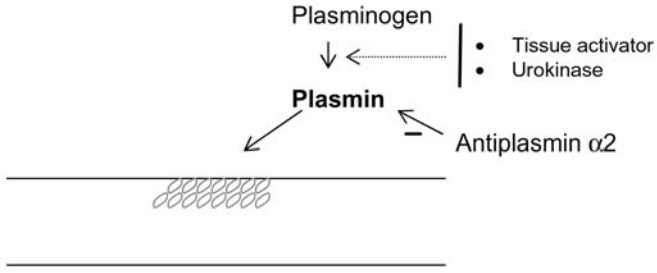

Figure 4. Fifth (fibrinolysis) phase of the hemostatic process.

by an alteration in platelet adherence to the exposed vascular endothelium and a lack of F VIII activation due to the deficiency of a plasma protein called Von Willebrand factor (vWF) (Qualitative and not simply quantitative alterations in vWF have recently also been described.); and (c) hemophilia B (F IX deficiency), also known as 'Christmas disease' (Scully and Cawson, 2004).

Deficiencies of the so-called 'contact factors' that trigger the intrinsic coagulation cascade are rare and generally benign, while extrinsic and common pathway factor deficiencies are also rare but can cause important bleeding.

Fibrin Formation

Fibrin forms a network that stabilizes the newly formed platelet clot and facilitates cell growth and regeneration of the damaged tissue. The action of thrombin is intrinsically limited, thus ensuring that the clotting process does not extend beyond the strict requirements of stopping hemorrhage and restoring vessel integrity. Such limiting action is exerted by thrombin itself, through the activation of a receptor located in the endothelial cell membrane and known as thrombomodulin. From the moment of thrombin binding to this receptor, a potent coagulation inhibitor, termed 'protein C', is produced (Norris, 2003).

Fibrin formation disorders may arise due to a lack of the fibrinogen precursor; when such a deficiency is partial, the condition is known as 'hypofibrinogenemia' (Awasthy *et al.*, 2004), while a total lack of fibrinogen (factor I) is referred to as 'afibrinogenemia' (Neerman-Arbez, 2001). Altered fibrin function may also result from qualitative fibrinogen alterations (dysfibrinogenemia) (Yamanaka *et al.*, 2003). These pathologies, and factor XIII (fibrin stabilizing factor) deficiency (Merchant *et al.*, 1992), are inherited on an autosomal basis and are characterized by a subject's tendency to hemorrhage.

Blood Clot Destruction

While blood clot formation is necessary to stem bleeding and regenerate damaged vascular endothelium, its persistence would be damaging. A physiological mechanism termed 'fibrinolysis' is responsible for destroying the blood clot, a process which begins when the plasma protein plasminogen is activated to plasmin (a protease). Such conversion is induced by two activators: tissue plasminogen activator (tPA) and urokinase. Activation in this sense takes place directly at the site of the blood clot. In turn, and with the purpose of preventing excessive fibrinolysis (which would imply bleeding risk), the body produces antiplasmin-alpha 2, which inhibits plasmin action (Nilsson, 1987; Diethorn and Weld, 1989). Fibrinolytic action can be prevented by the use of anti-fibrinolytic agents, such as ε-aminocaproic acid (EACA) or tranexamic acid, which attract plasminogen and plasmin, and avoid activation of plasminogen. Patients with antiplasmin-alpha 2 deficiency are characterized by a hemorrhagic tendency secondary to excess fibrinolysis (Fig. 4) (Favier *et al.*, 2001).

Independently of fibrinolysis proper, continued blood clot formation must also be contained. To this effect, protein C (activated through the thrombin-thrombomodulin complex) mediates the inactivation of factors V and VIII. Protein C, a potent anticoagulant, is assisted in its function by protein S, which further fragments factors V and VIII. Another plasma protein, antithrombin III, in turn inhibits thrombin. Qualitative or quantitative alterations of protein C, protein S, or anti-thrombin III can lead to a hereditary tendency to thrombosis (Norris, 2003).

The hereditary coagulation disorders thus include the following:

- Hemophilia A
- Von Willebrand's disease
- Hemophilia B
- Contact factor deficiencies
- Extrinsic and common pathway factor deficiencies
- Anomalies in fibrinogen-to-fibrin conversion
- Hereditary thrombotic tendencies

HEMOPHILIA A (FACTOR VIII DEFICIENCY)

Hemophilia A is the most common hereditary coagulation disorder, affecting 1/5000 males born live. The condition can be classified as severe (less than 1% of normal factor VIII

activity), moderate (1-5% of normal activity), or mild (5-25% of normal activity).

In these patients, hemostasis dependent upon blood vessel and platelet function is intact. The most common cause of bleeding in patients with hemophilia A is trauma, which increases as the child increases physical activity (Scully and Cawson, 2004).

Spontaneous bleeding has been reported in such patients under conditions of emotional stress, as during examinations or family arguments. In this sense, the dental professional should consider the possibility of bleeding as a result of the stress associated with dental treatment. A question has thus been raised as to whether anxiolytic medication should be provided for the dental treatment of such patients. The clinical manifestation is bleeding, particularly in the form of hemarthrosis, which can affect any body joint, including the temporomandibular joint (TMJ) (Alcalay and Deplas, 2002; Roosendaal and Lafeber, 2003). Bleeding located in the pharynx or neck can lead to airway obstruction. The laboratory parameters in such patients reveal a normal prothrombin time (PT) and a prolonged activated partial thromboplastin time (aPTT). Unlike in Von Willebrand's disease, the bleeding time is normal.

Bleeding of any kind in such individuals may require factor VIII replacement therapy, with the deficient factor administered, preferably, as recombinant factor VIII (or alternatively as cryoprecipitate). Desmopressin cover just before surgery, repeated every 12 hrs if necessary for up to 4 days, is useful to cover minor surgery in some very mild hemophiliacs. Desmopressin can be given as an intranasal spray of 1.5 mg desmopressin *per* mL with each 0.1-mL pump spray, or as a slow intravenous infusion, over 20 min, of 0.3-0.5 μg/kg. Tranexamic acid significantly reduces blood losses after surgery in patients with hemophilia and can be used topically or systemically. Systemically, it is given in a dose of 1 g (30 mg/kg) orally, 4 times daily, starting at least 1 hr pre-operatively for surgical procedures, or as an infusion (10 mg/kg in 20 mL normal saline over 20 min), then 1 gm tds orally for 5 days (child dose is 20 mg/kg) (Kasper, 2000).

A serious problem with older patients is the risk of viral contamination, particularly hepatitis C (HCV) and human immunodeficiency virus (HIV) (Lee and Dusheiko, 2002; Wilde, 2004). It must be taken into account that patients with hemophilia A require life-long F VIII replacement therapy to some degree, depending on the severity of the disease and the type of physical activity involved. In this sense, non-predictable trauma or accidents must also be taken into account.

To avoid viral contamination from blood, hematologists have designed treatment strategies for hemophilia A that avoid the use of blood or blood products. Dental professionals can benefit considerably from such strategies when planning dental treatment. Thus, desmopressin transiently elevates factor VIII concentrations, while ε-aminocaproic acid (EACA) and tranexamic acid minimize bleeding (Sindet-Pedersen *et al.*, 1988; Cattaneo, 1997).

As with all replacement therapies, it is important that the dental professional know the half-life of each of the different factors used. This aspect is central to our dental treatment plan at all times. The half-life of F VIII is 10-12 hrs, which indicates that the dental treatment sessions should be comprised of extensive treatments grouped on consecutive days (as few as possible) (Morfini *et al.*, 1991).

Table 2. Half-lives of the Coagulation Factors

Factor	Half-life
Factor VIII	10-12 hrs
Factor IX	48 hrs
Factor XI	72 hrs
Factor VII	2-6 hrs
Factor X	24-48 hrs
Factor II	48 hrs
Factor V	12-36 hrs
Fibrinogen	4 days
Factor XIII	12 days

The programming of dental treatment therefore depends on the half-life of the affected blood coagulation factor (Table 2). The presence of hemarthrosis of the temporomandibular joint requires immobilization of the latter with the application of ice. The joint should not be aspirated, unless the patient suffers great pain and tension; rather, in such situations, F VIII must be administered first, and functional rehabilitation of the temporomandibular joint should then be provided.

At all times, the patient must be aware of the importance of oral health, to avoid problems related to his hemophilia (Harrington, 2000). Depending on the anatomical location, bleeding in the oral cavity can be life-threatening. Puncture anesthesia must *never* be carried out without the administration of F VIII (Larson *et al.*, 1980). If a tooth extraction or some other hemorrhagic procedure is planned, the hematologist must first be consulted to decide the amount of F VIII replacement therapy required, and for how long (Zanon *et al.*, 2000; Piot *et al.*, 2002). The presence of inflammatory/painful processes in the mouth requires the dental professional to make sensible use of anti-inflammatory drugs/analgesics. However, most non-steroidal anti-inflammatory drugs (NSAIDs) are contra-indicated in hemophilic patients because of those drugs' anti-platelet action. Only acetaminophen (paracetamol), codeine, and, in some cases, ibuprofen can be used (provided that no prolonged bleeding occurs) (Stubbs and Lloyd, 2001; Brewer *et al.*, 2003).

It is known that about 15% of these patients can develop antibodies against F VIII, a problem which may be resolved, to a point, by the hematologist by using more F VIII, or, if there are no religious or cultural objections, by using anti-hemophilic factor A (of porcine origin) (Bayry *et al.*, 2003; Giangrande, 2003).

The prognosis for these patients depends on their incapacity, antibodies against F VIII, hepatitis, and liver cirrhosis, and the presence or absence of HIV/AIDS.

The presence of liver cirrhosis may require liver transplantation. In this respect, transplantation also resolves the hemophilia, since the donor liver is able to produce normal F VIII concentrations (Franchini *et al.*, 2002).

VON WILLEBRAND'S DISEASE

Von Willebrand's disease is a hereditary coagulation disorder characterized by a deficient or abnormal plasma protein known as the Von Willebrand factor (vWF), the physiological role of

which is to stabilize F VIII and mediate platelet adherence (Meyer *et al.*, 1991; Takahashi, 1993). Thus, F VIII levels are low. The bleeding associated with the disease is of variable intensity. For example, in the less severe presentations, bleeding tendency may manifest following tooth extraction. This hemorrhagic tendency decreases as the patient becomes older (Scully and Cawson, 2004).

Von Willebrand's disease is characterized by low concentrations of F VIII, and a prolonged bleeding time. The disorder is classified as follows:

Type 1 (quantitative alterations of Von Willebrand factor)

vWF concentration is below normal, the bleeding time and aPTT are prolonged, and F VIII concentrations are low.

Type 2 (qualitative alterations of Von Willebrand factor)

vWF concentration is not below normal, but the factor is unable to stabilize F VIII and aggregate platelets, and thus bleeding time and aPTT are prolonged, and F VIII concentrations are low.

Treatment in Von Willebrand's disease consists of the administration of a cryoprecipitate containing both vWF and factor VIII (Mannucci, 1998; Schneppenheim and Budde, 2004). Recently, desmopressin has been shown to be very effective in the management of these patients, since it is able to release vWF and plasminogen activator from the endothelial cells (Cattaneo, 1997). The administration of ε-aminocaproic acid (EACA) or tranexamic acid suppresses fibrinolysis. In dental treatments, it is possible to use EACA for prophylactic purposes at a dose of 20 mg/kg body weight (bw)/8 hrs, starting on the day before the intervention and prolonging administration until the surgical wounds have healed (Stubbs and Lloyd, 2001; Piot *et al.*, 2002).

HEMOPHILIA B (FACTOR IX DEFICIENCY)

This form of hemophilia is much less common than hemophilia A, and affects only 1/300,000 males born live. However, the clinical picture is very similar to that of hemophilia A, with a prolongation of aPTT. Some hemophilia B patients present an abnormal factor IX that slightly prolongs PT. Treatment consists of F IX replacement therapy; the half-life of this factor is two days—a fact that facilitates dental treatment (Scully and Cawson, 2004).

The dental management of patients with hemophilia B is practically the same as in the case of hemophilia A, though several extra precautions are required. In effect, and as an example, replacement therapy prescribed by the hematologist may consist of purified F IX or, alternatively, the so-called 'prothrombin complex'—a combination of 6 vitamin-K-dependent factors, F II, VII, IX, and X, and proteins C and S (Leissinger, 1999). It should be taken into account that administration of the prothrombin complex entails a certain thrombo-embolic tendency, and if the dental professional, in turn, administers ε-aminocaproic acid (EACA), this thrombo-embolic tendency is accentuated (Djulbegovic *et al.*, 1996). The use of EACA and tranexamic acid is therefore contraindicated in such situations.

CONTACT FACTOR DEFICIENCIES

Deficiency of Factor XII (Hageman factor), Pre-kallikrein

This is a generally benign disorder diagnosed when a prolonged aPTT is diagnosed. Factors XI, IX, and VIII are normal. Patients with Factor XII deficiency rarely show signs of hemorrhage, so no cover is needed (McDonough and Nelson, 1989; Harper and Friedland, 1992).

Factor XI Deficiency

This is a rare disorder (1/1,000,000) except in certain Jewish population groups, where the frequency jumps to 1/500. Severe factor XI deficiency (equivalent to less than 20-30% of the normal concentration) prolongs aPTT.

Replacement therapy is provided by the use of fresh-frozen plasma (FFP). The half-life of factor XI is 72 hrs (Blanchard *et al.*, 1996).

EXTRINSIC AND COMMON PATHWAY FACTOR DEFICIENCIES

This section includes deficiencies affecting factors VII, X, V, and II.

Factor VII (proconvertin) Deficiency

Factor VII deficiency is characterized by mild mucosal bleeding, which may appear without important prior antecedents following tooth extraction—both at the site of the actual extraction and at the anesthesia injection site, in the form of intramuscular hemorrhage (Tuddenham *et al.*, 1995). PT is prolonged, while aPTT appears normal.

The bleeding is managed with plasma, which possesses a half-life of 2-6 hrs (Divanon *et al.*, 2002; Eskandari *et al.*, 2002). Continuous infusion is thus required to ensure safe dental treatment, and the latter should be completed as quickly as possible, so that neither the dental intervention nor the hematological treatment will be excessively prolonged. Prothrombin complex can also be used, although, as has been mentioned above, it may induce a thrombo-embolic tendency. Antifibrinolytics are therefore contraindicated.

Factor X (Stuart-Prower factor) Deficiency

The clinical picture is similar to that of Factor VII deficiency, although, in this case, the laboratory findings reveal prolongation of both PT and aPTT. Fresh plasma with a half-life of 24-48 hrs is used in such patients (Knight *et al.*, 1985; Kouides and Kulzer, 2001; Uprichard and Perry, 2002).

Factor II (prothrombin) Deficiency

Bleeding in patients with factor II (prothrombin) deficiency appears when F II activity is less than 20% of its normal level, and can be mild or severe. PT and aPTT are prolonged, while thrombin time is normal.

Treatment consists of the administration of fresh plasma, though only every two days, since the half-life of factor II is 48 hrs—an interval that easily allows for the completion of dental management (Girolami *et al.*, 1998; Sun *et al.*, 1998).

Global Vitamin-K-dependent Factor Deficiency

Global vitamin-K-dependent factor deficiency is a rare condition in adolescents and adults, and is typically detected in nursing infants with bleeding, prolonged PT and aPTT, and low concentrations (less than 5% of the normal level) of factors II, VII, IX, and X (Brenner, 2000; Mousallem *et al.*, 2001).

These patients then require the life-long administration of 10 mg/24 hrs of vitamin K, which increases the concentrations of the deficient factors to 30-40% of their normal values. Dental treatment rarely poses a problem, and no special measures are required (Goraya, 2001).

Factor V (accelerator globulin) Deficiency

Factor V deficiency manifests with nasal and/or oral mucosal bleeding. Both aPTT and PT are prolonged. In 33% of patients, the bleeding time is prolonged, though the reason is unclear.

Replacement therapy consists of fresh plasma; older plasma is useless, since the protein associated with factor V is very labile. Concentrations of over 25% the normal level should be attained. The half-life of factor V is 12-36 hrs (Badurowa *et al.*, 1983; Sallah *et al.*, 1996). Platelet concentrates can also be used, since they contain 10-20% of the factor V found in blood.

ABNORMALITIES IN FIBRINOGEN-TO-FIBRIN CONVERSION

Fibrinogen Alterations

Patients with afibrinogenemia or hypofibrinogenemia have variable bleeding tendencies. It is not clear why some patients tend to experience mild bleeding, while others show a very strong tendency to bleed, to the point that death may result at an early age secondary to intracranial hemorrhage. Bleeding time is prolonged. Replacement is provided with cryoprecipitates (Cillo *et al.*, 2001; Neerman-Arbez, 2001; Awasthy *et al.*, 2004).

Dysfibrinogenemia is characterized by a qualitative alteration of fibrinogen, which may be present in normal amounts in blood. The patients tend to be asymptomatic, and bleeding may manifest only after major trauma or surgery (Deering *et al.*, 2003). In other patients, the initial manifestation is wound dehiscence, or a thrombotic tendency.

Treatment is with cryoprecipitate, affording a half-life of four days. Replacement therapy is to be continued in such patients until two days after bleeding has stopped.

Factor XIII (fibrin-stabilizing factor) Deficiency

When the concentration of factor XIII falls to less than 1-2% of its normal value, bleeding may arise. The disorder is typically diagnosed at a very early age, and sometimes at birth. In addition to a bleeding tendency, wounds tend to heal poorly. Intracranial hemorrhage in response to minor trauma is frequent.

Since there are no alterations in thrombin formation or in conversion from fibrinogen to fibrin, these patients show no alterations in PT, aPTT, or bleeding time (Merchant *et al.*, 1992; Egbring *et al.*, 1996). Treatment consists of fresh plasma, with the goal of reaching 5-10% of the normal F XIII concentration. The half-life of factor XIII is 12 days, *i.e.*, more than enough time for dental management to be completed (Daly and Haddon, 1988; Kobayashi *et al.*, 1990).

Antiplasmin-alpha 2 Deficiency

Antiplasmin-alpha 2 deficiency presents with a bleeding tendency similar to that in patients with hemophilia A. The clinical manifestations consist of prolonged bleeding following dental extraction, and the appearance of ecchymosis secondary to trauma (as, for example, in the areas over which removable partial dentures are placed). The use of anti-fibrinolytics before and after dental treatment reduces this tendency (Favier *et al.*, 2001; Nakahara and Koyama, 2003).

HEREDITARY TENDENCY TO THROMBOSIS

Quantitative and qualitative alterations in protein C, protein S, antithrombin III, or factor V produce a tendency to thrombosis.

Protein C Deficiency

Some patients are selected for anticoagulant therapy with warfarin, due to the reduction in protein C levels (though not all patients thus affected show the same tendency to develop thrombosis). Anticoagulant therapy could then complicate dental treatment. In this context, control of the international normalized ratio (INR) is essential, a ratio of 1.5-2.5 being the usual therapeutic range (Pescatore, 2001; Gatti *et al.*, 2003).

Protein S Deficiency

This condition is very similar to protein C deficiency (Crean *et al.*, 2000).

Antithrombin III Deficiency

When these patients develop acute thrombosis, the treatment of choice is heparin. Fresh plasma or an anti-thrombin III concentrate can also be used. The half-life of the latter is 16-24 hrs. Such individuals normally present with warfarin-type anti-coagulation once the acute phase of thrombosis has passed (del Rey López and Alonso Chico, 2002; Okamoto and Minami, 2003).

Alterations in Factor V (accelerator globulin) (resistance to activated protein C)

The most frequent hereditary predisposition to thrombosis is represented by the so-called 'Leiden mutation' of factor V, which results in factor V becoming resistant to inactivation by activated protein C (APC). The coagulation cascade thus loses one of its control mechanisms, with a resulting tendency to thrombosis. The clinical management of these patients is with anticoagulants (Dahlback, 2003; Montiel-Manzano *et al.*, 2003).

SUMMARY

Hereditary alterations of blood coagulation and other factors involved in hemostasis can lead to mild or severe bleeding tendencies, or, occasionally, to thromboses (spontaneous or following dental treatment). The management of such patients cannot be based on a single rigid protocol; each hematological disorder and individual patients may require an individualized approach. For this reason, the dental professional must consider numerous aspects when treating these patients:

(1) the type of hereditary hematological disorder involved;
(2) the treatment approach to the disorder;
(3) evaluation of whether the standard treatment should be modified as a consequence of the dental treatment requirements;
(4) evaluation of whether such modification will involve replacement therapy or drugs capable of increasing the level of the deficient factor;
(5) evaluation of drugs that may be contraindicated;
(6) the half-life of the transfused factor;
(7) evaluation of dental care planning and implementation according to the half-life of the transfused factor; and
(8) evaluation of whether conversion to heparin with INR control is necessary if the patient is receiving warfarin-type oral anticoagulation.

While all these aspects are relevant, priority should be given to the half-life of the factors. In patients deficient in factor VII (half-life, 2-6 hrs) or factor VIII (half-life, 10-12

hrs), it is rarely possible for dental procedures to be carried out (in terms of both amount and intensity) without the need for multiple patient visits requiring costly coagulation factor replacement therapy that becomes increasingly expensive, since the transfused amounts must be increased as the patient develops antibodies against the factor. In these patients, the deficient factor must be replaced strictly as required, so that the treatment remains efficacious in situations in which the patient's life is at risk.

This approach changes radically in patients with hereditary defects in which the replaced factor has a half-life of several days. In such situations, a single dose of the deficient factor may be adequate to allow for the completion of all dental treatment.

ACKNOWLEDGMENTS

This work was supported by CTS-263 from the Andalusia Regional Education Council, Spain, and from one commercial source (Implant Microdent System, Spain).

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