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Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers

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Summary. Excessive bleeding after dental procedures are one of the most frequent complications occurring in patients with hereditary bleeding disorders. In this retrospective study we collected data from 10 years of experience in the oral care of patients with congenital haemorrhagic disorders in three Italian Hemophilia Centers. Between 1993 and 2003, 247 patients with inherited bleeding disorders underwent 534 dental procedures including 133 periodontal treatments, 41 conservative dentistry procedures, 72 endodontic treatments and 288 oral surgery procedures. We recorded 10 bleeding complications (1.9%), most of which occurred in patients with severe/moderate haemophilia A undergoing multiple dental extractions. Thus, our protocol of management of patients with hereditary bleeding tendency undergoing oral treatment or surgery has been shown to be effective in preventing haemorrhagic complications.

Keywords: bleeding, haemophilia, oral surgery, therapy, von Willebrand's disease

Introduction

Adults with congenital bleeding disorders from a particular group of patients with an increased risk of excessive bleeding after dental procedures [1–4]. In particular, oral surgery has been complicated in the past by severe, often life-threatening, haemorrhages [2,5]. Starting from the 1970s, the introduction of clotting factor concentrates, desmopressin (DDAVP) and antifibrinolytic agents has significantly reduced the number of bleeding complications after dental treatments in such patients [6–12]. However, in spite of dental care being considered a priority problem in patients with a hereditary bleeding tendency [13–15], only a few studies on limited numbers of patients are available in the literature regarding the dental management of such patients [16–19].

In this retrospective study, we report the results of a survey of dental treatment carried out on 247 consecutive adult patients with inherited bleeding disorders followed at three Italian Hemophilia Centers (Trento, Verona and Parma) between 1993 and 2003.

Patients and methods

The series consisted of 247 consecutive adult patients (median age 37.4 years, range: 16–72; 163 males and 84 females, M/F ratio 1.9) who underwent 534 dental procedures between 1993 and 2003. Table 1 reports the main characteristics of these patients. Of the 247 patients, 121 had haemophilia A [which was severe (factor VIII < 1%) in 44 cases, moderate (FVIII between 1 and 5%) in 21 and mild (FVIII > 5%) in 56]. Fourteen patients had haemophilia B (four severe, five moderate and five mild), 95 patients were affected by von Willebrand's disease

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Table 1. Characteristics of the 247 patients with hereditary bleeding disorders included in the study.

Characteristics	Number of patients ($n = 247$)
Age [years; median (range)]	37.4 (16–72)
Males	163 (66.0)
Females	84 (34.0)
M/F ratio	1.9
Diseases	
Mild haemophilia A	56 (22.7)
Moderate haemophilia A	21 (8.5)
Severe haemophilia A	44 (17.8)
Mild haemophilia B	5 (2.0)
Moderate haemophilia B	5 (2.0)
Severe haemophilia B	4 (1.6)
von Willebrand's disease type 1	67 (26.1)
von Willebrand's disease type 2	26 (10.5)
von Willebrand's disease type 3	2 (0.8)
Factor XI deficiency	5 (2.0)
Factor VII deficiency	3 (1.2)
Factor XIII deficiency	1 (0.4)
Haemophilia A carrier	4 (1.6)
Storage pool disease	2 (0.8)
Aspirin-like disease	2 (0.8)

(VWD), five patients by FXI deficiency, three by FVII deficiency, one by FXIII deficiency, four by platelet disorders (three storage pool disease, one aspirin-like disease) and four patients were carriers of haemophilia A. Three patients (all with severe haemophilia A) had a inhibitor to FVIII. The 534 dental procedures were 133 periodontal treatments, 41 conservative dentistry procedures, 72 endodontic treatments and 288 oral surgery procedures. Most of the periodontal treatments were performed as preparation therapy before oral surgery. Table 2 describes the type of interventions, according to the diagnosis of the bleeding disorder. For each intervention, we recorded the type, the dose and the duration of the local and/or systemic therapies. The treatments and dosing regimens used for the different interventions were those approved by the Italian Association of Hemophilia Centers (AICE) [20–22]. Local haemostatic treatment included antifibrinolytic agents [tranexamic acid, Tranex (Malesci, Florence, Italy), Ugurol, (Bayer, Berkeley, CA, USA)] and/or fibrin glue (Tissucol, Immuno, Pisa, Italy). The fibrin glue was used for dental extractions and was prepared by mixing the contents of two syringes, one containing thrombin and calcium chloride and the second containing fibrinogen, FXIII and aprotinin. Thrombin converts fibrinogen into an unstable fibrin clot, FXIII stabilizes the clot and aprotinin prevents its degradation. In most cases, 0.5 mL of fibrin glue was applied to the wall of the socket. Systemic therapies included oral tranexamic acid, s.c. DDAVP (Emosint, Kedrion, Lucca, Italy) and i.v. infusion of coagulation factor concentrates or fresh-frozen plasma. Desmopressin, at a standard dose of 0.3 μg kg^{-1}, was administered s.c. 60 min before the surgical procedures in patients with type 1, type 2A VWD and mild haemophilia A who had previously been proven to be responsive to DDAVP [22]. Plasma-derived FVIII concentrates [Emoclot D.I. (Kedrion), Kryobulin (Immuno), Koate HS (Cutter, Sienna, Italy), Hemofil M (Baxter, Deerfield, IL, USA)], and recombinant FVIII (rFVIII) concentrates [Refacto (Wyeth, Madison, NJ, USA), Recombinate (Baxter), Kogenate^{TM} (Bayer) and Helixate (Aventis

Table 2. Type of dental procedures according to the diagnosis of the bleeding disorder.

Type of dental procedure ($n = 534$)	Hereditary bleeding disorders
Periodontal treatment ($n = 133$)	
Calculus removal ($n = 69$)	14 MHA; 3 HAM; 9 HAS; 1 MHB; 1 HBM; 1 HBS; 31 VWD1; 7 VWD2; 2 FVIID
Scaling and root planning ($n = 64$)	14 MHA; 1 HAM; 9 HAS; 1 MHB; 27 VWD1; 8 VWD2; 2 FXID; 2 HAC
Conservative dentistry procedures ($n = 41$)	12 MHA; 6 HAM; 13 HAS; 1 MHB; 2 HBM; 5 VWD1; 2 FVIID
Endodontic treatment ($n = 72$)	19 MHA; 7 HAM; 11 HAS; 1 MHB; 23 VWD1; 7 VWD2; 2 FXID; 2 HAC; 1 SPD
Oral surgery procedures ($n = 288$)	
Single dental extraction ($n = 121$)	31 MHA; 14 HAM; 18 HAS; 3 MHB; 3 HBS; 33 VWD1; 16 VWD2; 1 FXIII; 2 HAC
Multiple dental extractions ($n = 98$)	23 MHA; 8 HAM; 28 HAS; 2 HBM; 2 HBS; 24 VWD1; 7 VWD2; 1 VWD3; 2 HAC; 1 SPD
Retained teeth extraction ($n = 21$)*	2 MHA; 2 HAM; 3 HAS; 8 VWD1; 3 VWD2; 1 FXID; 1 HAC; 1 ALD
Periodontal surgery ($n = 19$)	4 MHA; 1 HAM; 4 HAS; 2 HBM; 3 VWD1; 4 VWD2; 1 FXID
Endodontic surgery ($n = 13$)	2 MHA; 1 HAS; 1 HBS; 5 VWD1; 2 VWD2; 1 VWD3; 1 ALD
Cystectomy ($n = 4$)	1 MHA; 1 HAM; 1 VWD2; 1 FXID
Abscess incision ($n = 2$)	1 HAS; 1 WVD1
Biopsy for leukoplakia ($n = 2$)	2 HAS
Implant ($n = 8$)	6 VWD1; 1 VWD2; 1 HAC

MHA, mild haemophilia A; HAM, moderate haemophilia A; HAS, severe haemophilia A; MHB, mild haemophilia B; HBM, moderate haemophilia B; HBS, severe haemophilia B; VWD1, von Willebrand's disease type 1; VWD2, von Willebrand disease's type 2; VWD3, von Willebrand's disease type 3; FXID, factor XI deficiency; FVIID, factor VII deficiency; FXIIID, factor XIII deficiency; HAC, carrier haemophilia A; SPD, storage pool disease; ALD, aspirin-like disease.

*15 single extractions and six multiple extractions.

Behring, Marburg, Germany)] were used for haemophilia A patients. Plasma-derived FIX concentrates [Aimafix D.I. (Kedrion), Bebulin (Immuno), Mononine (Aventis Behring)], and rFIX concentrates [BeneFix® (Wyeth)] were used for haemophilia B patients. The intermediate purity FVIII/von Willebrand factor (VWF) concentrate Haemate-P (Aventis Behring) was used for WVD patients. Factor VIII or FIX concentrates were infused 1 h prior to oral surgery at a dose such as to achieve a peak level above 30% of normal [22]. When nerve trunk infiltration was performed, the plasma level of coagulation factors was increased to 50%. Fibrogammin P (Aventis Behring) was utilized for the patient with FXIII deficiency.

For patients undergoing oral surgery, we also recorded the type of suture (resorbable or not) and the type of anaesthesia (general or local). Adjunctive antibiotic therapy with amoxicillin was given on the day of oral surgery and continued for 6 days. Paracetamol, occasionally combined with narcotic drugs, or ibuprofen were used for pain control. As regards concomitant viral infections, 132 patients (53.4%) were positive for hepatitis C virus (HCV) infection, 33 patients (13.4%) for hepatitis B virus (HBV) infection and 12 patients (4.9%) for human immunodeficiency virus (HIV) infection. Thirteen patients (5.3%) had a platelet count below the normal range because of liver cirrhosis (mean value $96.2 \pm 33.7 \times 10^9$ L^{-1}; normal range: 150–400×10^9 L^{-1}).

We documented any bleeding episodes and adverse drug reactions possibly associated with the prophylactic treatment. Treatment outcome was rated as excellent (achievement of normal haemostasis), good (mildly abnormal haemostasis not requiring additional therapy), or poor (haemostasis less than expected) as a measure of overall efficacy.

We used Student's *t*-test to analyse normally distributed continuous data and the chi-square or Fisher's exact test to analyse categorical data. A *P*-value of <0.05 was considered statistically significant.

Results

Type of prophylactic regimen

As regards non-surgical procedures, most of the 133 periodontal treatments were managed only with tranexamic acid mouthwashes (10 mL of 5% solution for 2 min) four times a day for 4–8 days (median 5.4 days) after the procedure. Additional systemic therapy with oral tranexamic acid (1 g given orally three times a day for at least 5 days after the procedure) was used for 19 patients undergoing deep scaling. Of these 12 patients with more severe coagulation defects were also managed with other systemic therapies: two patients with VWD type 1 received a further single administration of DDAVP (0.3 μg kg^{-1} administered s.c. 1 h before the procedure), whereas 10 patients (six with severe haemophilia A, three with VWD type 1 and one with VWD type 2) received clotting factor concentrates (the patients with haemophilia A received a mean dose of 2216.7 ± 417.4 IU of FVIII concentrate and a mean number of 1.5 ± 0.5 infusions per procedure, whereas the patients with VWD were treated with a single dose of VWF/FVIII concentrate, infused i.v. 30 min before surgery: the mean dose of the concentrate was 1500.1 ± 288.6 IU.

The great majority of the 113 conservative and endodontic procedures were managed only with local antifibrinolytic agents (mouthwashes of tranexamic acid, 10 mL of 5% solution for 2 min) four times a day for 4–8 days (median 5.7 days) after the procedure. However, when the cavities extended to the gingival and instrumentation could cause gingival bleeding, additional systemic antifibrinolytic treatment was used [nine patients received 1 g of tranexamic acid given orally three times a day for 5–8 days (median 5.4 days) after the procedure]. Moreover, five patients undergoing plexic anaesthesia received other systemic treatments (two patients with type 1 VWD were treated with a single dose of DDAVP given s.c. at a dose of 0.3 μg kg^{-1} and three patients with severe haemophilia A received a mean single dose of FVIII concentrate of 1833.3 ± 288.7 IU).

As regards the 288 oral surgery procedures, a combination of systemic and local antifibrinolytic treatment was used. The usual regimen consisted of 1 g of tranexamic acid given orally four times a day for 7 days after the procedure, combined with tranexamic acid mouthwashes (10 mL of 5% solution for 2 min) four times a day for 7 days following surgery. Additional local therapy with fibrin glue was applied by the oral surgeons in 159 cases (55.2%), most of which were multiple or retained dental extractions. A non-resorbable silk suture was applied in all cases. In all cases, local anaesthesia was performed. Anaesthesia by plexic or intraligamentous infiltration was chosen in 147 (51.0%) and 92 (31.9%) cases, respectively, while nerve root trunk infiltration was chosen in the remaining 49 (17.1%) cases. A vasoconstrictor (adrenaline) was added to the local anaesthesia in nearly half of the oral surgery procedures (134 of 288 cases, 46.5%). Systemic therapy with s.c. DDAVP (each dose being

0.3 μg kg^{-1}) was used in 91 cases (31.6%; 47 patients with type 1 VWD, 14 patients with type 2A VWD, 18 patients with mild haemophilia A, six carriers of haemophilia A, two patients with FXI deficiency, two patients with storage pool disease and two patients with aspirin-like disease) with a mean number of 1.6 ± 0.7 of administrations per procedure. In the remaining 197 cases, FVIII concentrates were used in 119 patients with haemophilia A (mean dose infused of FVIII concentrate: 2284.3 ± 744.7 IU; mean number of infusions per procedure: 1.8 ± 1.0), FVIII/VWF concentrates were used in 55 patients with VWD (mean dose of FVIII/VWF concentrate infused: 1511.2 ± 412.1 IU; mean number of infusions per procedure: 1.3 ± 0.7), FIX concentrates were used in 21 patients with haemophilia B (mean dose of FIX concentrate infused: 2166.7 ± 505.5 IU; mean number of infusions per procedure: 1.3 ± 0.5), FXIII (20 IU kg^{-1}) was infused in one patient with FXIII deficiency and fresh-frozen plasma (20 mL kg^{-1}) was transfused in a patient with FXI deficiency.

On the whole, 304 procedures were managed with additional systemic therapies including DDAVP (94 procedures), coagulation factor concentrates (209 procedures) or fresh-frozen plasma (one procedure).

Type of bleeding episodes

We recorded 10 (1.9%) bleeding complications, most (seven cases) of which occurred in patients after multiple dental extractions and with severe/moderate haemophilia A (six cases). One case occurred after a single dental extraction, one case after an implant and one case after deep scaling. In all the remaining procedures the prophylaxis outcome was rated as excellent/good. Table 3 reports the bleeding complications and the treatment for each episode. In all cases, local and systemic therapies effectively controlled the haemorrhages. No bleeding event required hospitalization. Bleeding events developed a median of 5.7 days (range: 3–12) after the oral procedure. Fibrin glue was used in six cases, whereas additional systemic therapy (antifibrinolytic drugs and/or DDAVP and/or coagulation factor concentrates) was utilized in all cases. We did not record a statistically significant higher incidence of bleeding complications in patients with a platelet count below the normal range or with inhibitors. Similarly, we did not document differences in the rate of oral surgery-related bleeding episodes according to the different types of local anaesthesia used or between patients treated or not with vasoconstrictors.

Other complications

No adverse drug reactions or thrombotic episodes were observed following the local and systemic treatments. We did not record any infectious complications after the oral treatments or surgery. The incidence of postoral surgical complications did not differ between patients with or without HBV, HCV or HIV infections.

Discussion

Dental management of patients with hereditary bleeding disorders involves a close cooperation between haematologists and oral surgeons. In fact, the former must provide the latter with the appropriate prophylactic regimen to prevent secondary local bleeding during oral interventions. On the contrary, oral surgeons must carry out all techniques to reduce the probability of surgery-related bleeding [1,4,17,18,23,24]. The lack of large published retrospective or prospective studies supporting the recommended regimens for dental treatment of haemophiliacs spurred us to review our 10-year experience in the oral management of patients with hereditary haemorrhagic disorders. Thus, this report, collecting 534 consecutive dental procedures carried out in 247 patients with inherited bleeding disorders, is the largest study published so far in the medical literature. Moreover, more than 40% of the dental treatments reported are non-surgical procedures, for which very few data are available in the literature.

In the present study, we found a low incidence (1.9%) of bleeding complications after oral procedures. Even considering only oral surgery, the rate of bleeding events remained low (nine of 288, 3.1%), similar to that observed in the few studies published so far [16–18] and not different from that found in the normal healthy population [18]. In our opinion, the good results of our protocol are mainly due to the systematic use of local therapies with antifibrinolytic drugs (tranexamic acid) and fibrin glue. In fact, it has been demonstrated by several authors [25–36] that these agents, which actively improve local haemostasis, can significantly reduce the rate of systemic therapy use and of bleeding complications during oral surgery. Moreover, in the present study local therapies were a very useful support to systemic treatments for the effective management of bleeding complications.

Of note, one of the bleeding complications was recorded in a VWD patient after multiple implants. Although definitive conclusions can be drawn because of the small number of patients undergoing

Table 3. Type and treatment of bleeding episodes in the 534 oral procedures.

N	Diagnosis	Type of oral procedure	Local PX*	Systemic PX†	Days‡	Treatment of the bleeding episode
1	VWD1	Multiple dental extraction	TA + FG	TA + FVIII/VWF 1500 IU b.s.	+3	FG + FVIII/VWF 1500 IU day^{-1} for 2 days
2	HAS	Multiple dental extraction	TA + FG	TA + FVIII 3000 IU b.s. + 2000 IU day^{-1} for 2 days	+12	FG + TA§ 1 g × 4 day^{-1} for 5 days + FVIII 2500 IU day^{-1} for 2 days
3	HAS	Multiple dental extraction	TA + FG	TA + FVIII 2000 IU b.s. + 2000 IU after 12 h	+3	FG + FVIII 2000 IU
4	HAS	Multiple dental extraction	TA + FG	TA + FVIII 2500 IU b.s.	+10	FG + TA§ 1 g × 4 day^{-1} for 5 days + FVIII 2000 + 1500 IU after 12 h
5	HAM	Single dental extraction	TA	TA + FVIII 2000 IU b.s.	+3	FVIII 2000 IU
6	VWD1	Multiple dental extraction	TA + FG	TA + DDAVP 0.3 μg kg^{-1} b.s.	+5	FG + DDAVP 0.3 μg kg^{-1} day^{-1} for 2 days
7	HAS	Parodontal treatment	TA	TA + FVIII 1500 IU b.s.	+2	FVIII 2000 + 1500 IU after 12 h
8	HAC	Multiple dental extraction	TA + FG	TA + DDAVP 0.3 μg kg^{-1} b.s.	+5	FG + DDAVP 0.3 μg kg^{-1} for 2 days
9	HAM	Multiple dental extraction	TA + FG	TA + FVIII 2500 IU b.s.	+7	TA§ 1 g × 4 day^{-1} for 5 days + FVIII 1500 IU
10	VWD1	Multiple implants	TA	DDAVP 0.3 μg kg^{-1} b.s. + 0.3 μg kg^{-1} day^{-1} for 2 days	+7	TA§ 1 g × 4 day^{-1} for 7 days + DDAVP 0.3 mg kg^{-1} day^{-1} for 3 days

PX, prophylaxis; b.s., 1 h before surgery; VWD1, type 1 von Willebrand's disease; HAM, moderate haemophilia A; HAS, severe haemophilia A; HAC, haemophilia A carrier; TA, tranexamic acid; FG, fibrin glue; FVIII/VWF, factor VIII/von Willebrand factor concentrate; FVIII, factor VIII concentrate; DDAVP, desmopressin.

*Local prophylaxis with tranexamic acid consisted of mouthwashes (10 ml of 5% solution for 2 min) 4 times a day for 7 days following the procedure.

†Systemic prophylaxis with tranexamic acid consisted of 1 g given orally four times a day for 7 days after the procedure.

‡Days elapsed between the oral procedure and the onset of bleeding episode.

§Given orally and as mouthwashes.

implants evaluated in our study, we do advise further trials on larger series of patients in order to assess the safety of this procedure in haemophiliacs.

Finally, although more than half of the patients were positive for HCV, HBV or HIV infections, we did not find an increased rate of postoral surgical complications in patients with viral infections associated with their haemostatic defect, thus confirming previous observations by Scully *et al.* [19]. In particular, our protocol was effective in the management of oral surgery in HIV-infected haemophiliacs, whose bleeding tendency may be aggravated by the concomitant presence of thrombocytopenia and drugs or infections affecting the bone marrow, liver, clotting factors or platelets. Similarly, the concomitant presence of thrombocytopenia did not represent an additional risk factor for bleeding complications after dental procedures in our series.

In conclusion, the protocol for the dental management followed at our three haemophilia centres during these last 10 years has been demonstrated safe and effective, with low incidences of haemorrhagic and treatment-related complications.

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