THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 7

RESEARCH ARTICLE

RETROSPECTIVE STUDY OF A SURGICAL PROTOCOL, COMPLICATIONS AND SURVIVAL OF DENTAL IMPLANTS PLACED IN PATIENTS WITH VON WILLEBRAND DISEASE

Gatti, Patricio Cesar[1], Parreira, Miryam[1], Gualtieri, Félix Ariel[2], Puia, Sebastián Ariel[1]

[1]Department of Oral and Maxillofacial Surgery I of the School of Dentistry of Buenos Aires University, Marcelo T de Alvear 2142, C1122AAH, CABA, Argentina.
[2]Department of Legal and Forensic Dentistry and History of Dentistry of the School of Dentistry of Buenos Aires University, Marcelo T de Alvear 2142, C1122AAH, CABA, Argentina.

OPEN ACCESS

PUBLISHED
31 July 2024

CITATION
Gatti, P.C., Parreira, M., et al., 2024. Retrospective study of a surgical protocol, complications and survival of dental implants placed in patients with von willebrand disease. Medical Research Archives, [online] 12(7). https://doi.org/10.18103/mra.v12i7.5510

DOI
https://doi.org/10.18103/mra.v12i7.5510

ISSN
2375-1924

ABSTRACT

Von Willebrand's disease, described by Erik von Willebrand, is the most frequent hemorrhagic disorder. Its main symptom is mucosal bleeding. Willebrand's disease occurs due to a qualitative or quantitative defect of the von Willebrand factor molecule and follows an autosomal inheritance pattern. For dental implant placement, the treatment of hemorrhage caused by this disease requires close collaboration between hematologists and oral surgeons.

The aim of this study was to evaluate the clinical success rate of dental implants and the incidence of bleeding in patients with von Willebrand's disease when a local surgical protocol was applied, supported by systemic and local hemostatic measures. A retrospective study was performed between January 2018 and December 2023 on patients over 18 years old diagnosed with von Willebrand's disease. All patients had an interview with their hematologist to determine whether they needed a single preoperative dose of Desmopressin acetate. A surgical implant protocol was implemented, supported by systemic and local hemostatic measures. Data on age, sex, type of von Willebrand's disease, Desmopressin acetate administration, and whether implants were immediate or deferred, flapless or minimally invasive were collected from the medical records. The success rate was evaluated considering absence of pain, mobility and suppuration. Implant stability was measured using a resonance frequency analyzer (Osstell). Data were described by frequencies and percentages with 95% confidence intervals or summary measures, as appropriate. Twenty-eight surgeries were performed, placing 41 implants in 26 patients (23 females and 3 males), with a mean (range) age of 50.5 (23 to 72) years. Among the patients evaluated, 21 had type 1 von Willebrand's disease and one had type 2. No bleeding was recorded. Mean implant stability measured with the Osstell frequency analyzer was 71.

Implant stability and success rate in patients with Willebrand's disease was similar to that reported in other studies on patients without systemic disorders. Systemic and local protocols are essential to avoid complications and ensure successful treatment.

Introduction

Von Willebrand disease (VWD), described by Erik Von Willebrand, is the most common bleeding disorder. Its prevalence ranges from 1/100 to 1/10,000. The main symptoms are mucosal bleeding such as epistaxis, bleeding from the gastrointestinal tract, bleeding from the gums, menorrhagia and excessive bleeding after trauma or surgery. VWD occurs due to a qualitative or quantitative defect in the von Willebrand factor (VWF) molecule and follows an autosomal inheritance pattern. The VWF gene is located on the short arm of chromosome 12. The disease often first manifests after a dental procedure. If there is clinical suspicion for the diagnosis of VWD, specific VWF testing should be performed, as there are no good screening tests for this condition[1-3]. Recommended initial testing includes VWF:Ag, VWF:RCo, and FVIII:C. VWD is classified into 3 different types: type 1 (partial defect in the amount of VWF), type 2 (qualitative defects), and type 3 (total lack of VWF). Type 2 is further subdivided into 2A, 2B, 2M and 2N[4].

Von Willebrand disease affects both primary and secondary hemostasis. In primary hemostasis, VWF facilitates platelet adhesion to sites of vascular injury via the glycoprotein Ib receptor (GPIb). In addition, to achieve secondary hemostasis, VWF stabilizes and protects factor VIII[5,6].

For minor surgery, a clinical guideline published by Conell NT et al. suggests giving tranexamic acid alone over increasing VWF activity levels to >0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of >0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures such as the placement of a dental implant[7].

Davis A et al, evaluated the risk of bleeding in patients with hereditary bleeding disorders in patients undergoing gastro-intestinal endoscopic procedures. This study suggests that TXA without prophylactic factor replacement may be a safe approach for mild and moderate hereditary bleeding disorders patients undergoing standard risk endoscopic procedures[8].

For dental implants, the treatment of hemorrhage caused by this disease requires close collaboration between hematologists and oral surgeons. The frequency and severity of bleeding depends on the type of VWD, the type of surgery, and local factors such as gingival/periodontal inflammation[9]. This technique has advanced considerably in recent years, increasing its predictability and reaching broader segments of the population. Currently, dental implant treatment in patients with coagulation disorders is not an absolute contraindication for dental implant surgery, although these patients may be at risk for prolonged bleeding and blood loss[10].

Case reports on the subject are scarce and there is no consensus or treatment guidelines for implant treatment in these patients. In the last years, some authors have presented safe protocols for performing dental implants in patients with Von Willebrand and other haemorrhagic disorders[11-14].

The aim of this study was to evaluate complications and survival of dental implants placed in patients with von Willebrand disease when a surgical implant protocol was implemented.

Materials and Methods

A retrospective study was performed between July 2018 and January 2023 on patients over 18 years old diagnosed with VWD who were referred to the Department of Oral and Maxillofacial Surgery I of the School of Dentistry of Buenos Aires University for placement of dental implants. All patients provided a medical-dental history and the relevant clinical and imaging studies (panoramic radiographs and cone beam tomography). Before the surgery, they had an interview with their hematologist to determine whether they needed a single preoperative dose of Desmopressin acetate (DDAVP).

All of them had been diagnosed at the Hemostasis and Thrombosis service "Mariano Castex Hematological Research Institute", who had history

of dental or gynecological bleeding. The evaluation was carried out by estimation of the concentration of VWF in plasma (VWF:Ag); activity assessment (VWF:RCo, GPIb binding, anti-Domain A1 antibodies); determination of FVIII activity (FVIII:C); and indirect reflection of VWF function. (Table 1)

Table 1. Diagnosis

VWF:Ag	was determined by immunological techniques. The methods of choice are enzyme-linked immunoassays (ELISA) (high sensitivity: 0-5 UI/dL) or immuno-turbidimetric assays (LIA) (lower sensitivity: 5-10 UI/dL).
VWF ACTIVITY VWF:RCo.	It reflected the interaction of VWF with GPIb/IX/V. It is the test chosen to evaluate VWF activity. It is based on the property of VWF to agglutinate platelets in the presence of ristocetin in vitro and quantifying the agglutination produced. Alterations in HMWM or mutations in the VWF A1 domain lead to alterations in VWF:RCo levels. It is difficult to standardize, has a high intra- and inter-laboratory coefficient of variation (10-40%), especially at values <15 UI/dL, and has low sensitivity at levels <10 UI/dL. There are polymorphisms (p.Asp1472His), which can reduce binding to ristocetin and others (p.Ala1381Thr) have a greater affinity for GPIbá, which is why they give artificially low/high values of VWF:RCo.
FVIII:C	Measures coagulant activity. In the context of VWD evaluation, it is an indirect reflection of the ability of VWF to bind FVIII and stabilize its half-life. The most used methodology is the "one-stage" method (automated, semi-automated or manual
QUOTIENTS	VWF activity results should be analyzed together with VWF:Ag and FVIII:C levels for better diagnostic interpretation. In normal individuals, the FVIII/VWF ratio (FVIII/VWF:Ag; FVIII/VWF:RCo or FVIII/VWF:CB) is ¡Ö1. The same occurs for VWF:RCo/VWF:Ag and VWF:CB/VWF:Ag, where values <0.6 suggest the presence of dysfunctional VWF; however, the variability of VWF:RCo affects its usefulness. An FVIII/VWF:Ag ratio <0.6 suggests VWD2N or hemophilia.

Patients were instructed to perform mouth rinses with a solution of 0.12% chlorhexidine, beginning 48 hours prior to surgery, and to take 1 g of amoxicillin by mouth 1 hour before the procedure. All surgical steps were performed by two maxillofacial surgeons calibrated in the surgical technique, and with hemostatic measures. The implants were placed under local anesthesia. When flaps were made, minimally invasive surgery was performed; a mucoperiosteal flap was made exposing only the coronal portion of the alveolar ridge, avoiding vertical discharges. When the clinical and radiographic analysis showed sufficient bone thickness and height, and that there was enough attached gingiva, flapless surgery was performed. In cases where an extraction was required and the anatomical situation allowed it, the implant was placed at the same time using a healing abutment applied with a hemostatic sponge or similar product (bismuth subgallate or oxidised cellulose). A standard drilling protocol was followed to place dental implants. In all cases, cylindrical implants with internal connection were used (Q Implant, Buenos Aires, Argentina /Straumann SLA, Basel, Switzerland). Cross-stitch sutures were performed with 000 atraumatic braided nylon. The patients maintained a gauze pad soaked in tranexamic acid (TXA) over the

wound with occlusal pressure for 30 minutes and were immediately followed up for the evaluation of a possible occurrence of immediate hemorrhage. Then they were instructed to keep the gauze over the wound for one hour, eat a soft, cold diet for 48 hours, apply local intermittent cold, and avoid mouth rinses or salivation.

Patients were prescribed 500 mg of Paracetamol every eight hours for two days, and 500 mg of amoxicillin every eight hours for five days[15].

Data on age, sex, type of VWD, DDAVP administration, whether implants were immediate or deferred, flapless or minimally invasive, and occurrence of hemorrhage were collected from the medical records. Implant survival rate was evaluated considering absence of pain, suppuration, and clinical mobility as parameters at least 2 years after loading. Implant stability was measured using a resonance frequency analyzer (Osstell ISQ, W&H company, Goteborg, Sweden) by inserting the peg in the dental implant and placing the tip (without touching the peg) of the analyzer at 45° to the peg. ISQ (implant stability quotient) was measured in buccal and palatal aspects and the mean was used for statistical analysis[16].

All prostheses were made following the manufacturer's suggested protocol.

Categorical variables were described by absolute frequencies and percentages with 95% confidence intervals (95%CI) estimated using Wilson's method. The following measures were used to describe quantitative variables: mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum. The analysis was performed in R software (R Core Team, 2023) with DescTools (Signorell, 2023) and ggplot2 (Wickham, 2016) packages[17-19].

Results:

The study included 26 patients who underwent 28 surgeries in which 41 implants were placed.

Table 2 shows the characteristics of the 26 patients included in the study.

Variable	
Sex	
Female	23 (88%, 71 to 96)
Male	3 (12%, 4 to 29)
Age (yrs)	50 (13)
VWD (type)	
1	25 (96%, 81 to 99)
2	1 (4%, 1 to 19)
Smoker	
No	20 (77%, 58 to 89)
Yes	6 (23%, 11 to 42)

Regarding the type of VWD, 25 patients had type 1 (96%; 95%CI 81% to 99%), and only one patient (a 48-year-old male) had type 2 (4%; 95%CI 1% to 19%) (Figure 1). Pre-preparation with DDAVP was performed in 5 patients (19%; 95%CI: 9% to 38%), and not performed in 21 patients (81%; 95%CI: 62% to 91%), (Figure 2).

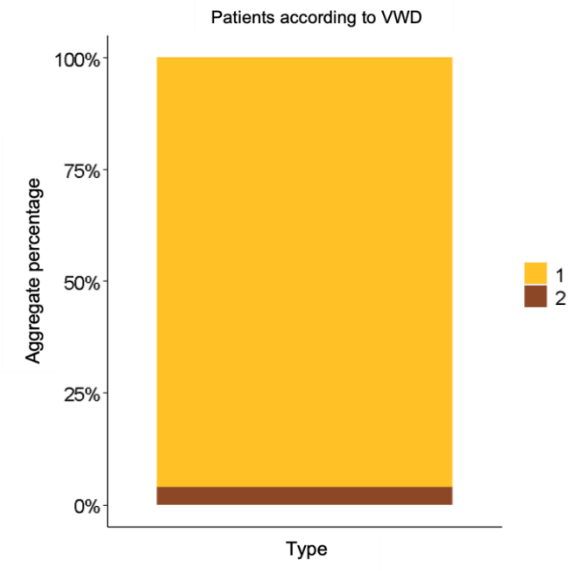

Figure 1. Distribution of patients according to type of von Willebrand disease (VWD).

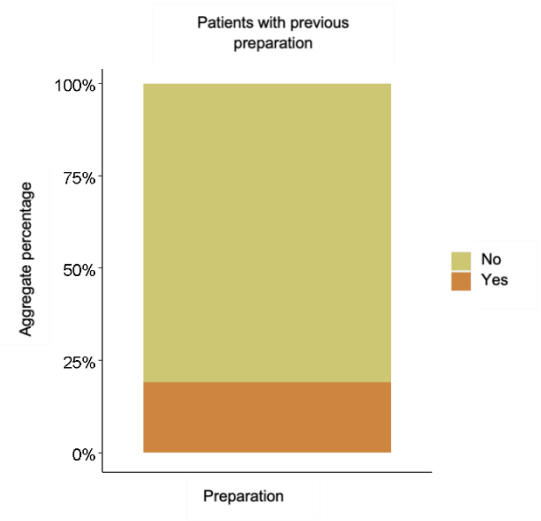

Figure 2. Distribution of patients according to use of previous preparation with DDAVP

The 28 surgeries performed (Figure 3) took 17 to 38 minutes, with a mean (SD) of 26 (7) and a median (Q1-Q3) of 25 (22-32). Flapless technique was used in 2 surgeries (7%; 95%CI: 2% to 23%), and minimally invasive technique in 26 (93%; 95%CI: 77% to 98%).

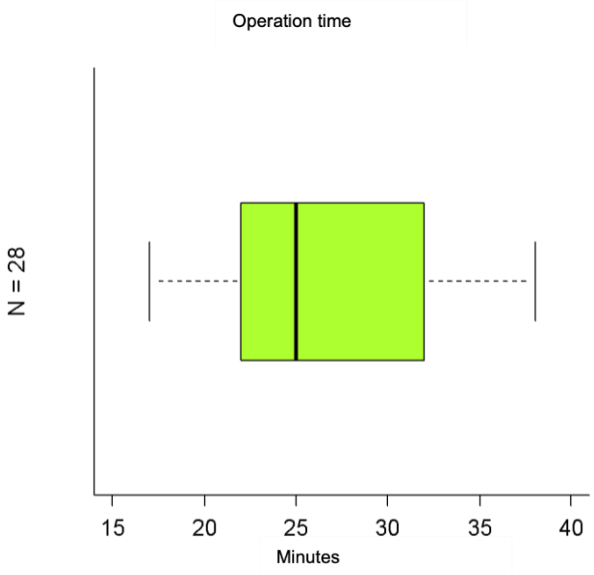

Figure 3. Distribution of surgeries according to duration. Box plot: extremes, minimum-maximum; edges, Q1-Q3; inner line, median

The most frequent among the 41 implants placed were upper second premolars (24%; 95%CI 14% to 39%) (Table 3). There were 31 delayed implants (76%; 95%CI 61% to 86%) and 10 immediate implants (24%; 95%CI 14% to 39%), (Figure 4).

Out of the total number of implants placed only 10 were Straumann, the other 31 were Q Implant.

Implant stability on the ISQ (Osstell) scale ranged from 63 to 75, with a mean (SD) of 71 (3) and a median (Q1-Q3) of 70 (69-73), (Figure 5).

Table 3. Distribution of implants by tooth. IC, central incisor; IL, lateral incisor; CA, canine; P1, first premolar; P2, second premolar; M1, first molar; M2, second molar.

Tooth	N (%, IC95)
Upper maxilla	
IC	2 (5%, 1 to 16)
IL	2 (5%, 1 to 16)
CA	1 (2%, 0 to 13)
P1	4 (10%, 4 to 23)
P2	10 (24%, 14 to 39)
M1	6 (15%, 7 to 28)
lower jaw	
IL	2 (5%, 1 to 16)
CA	2 (5%, 1 to 16)
P1	1 (2%, 0 to 13)
P2	2 (5%, 1 to 16)
M1	6 (15%, 7 to 28)
M2	3 (7%, 3 to 19)
Total	41 (100%)

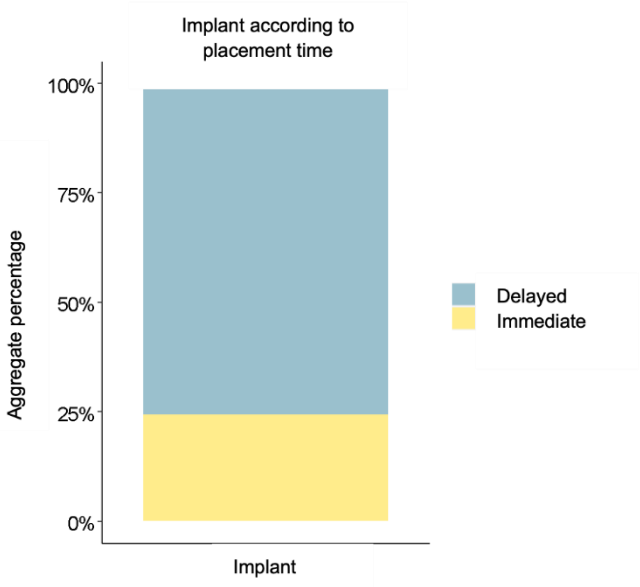

Figure 4. Distribution of implants according to placement time.

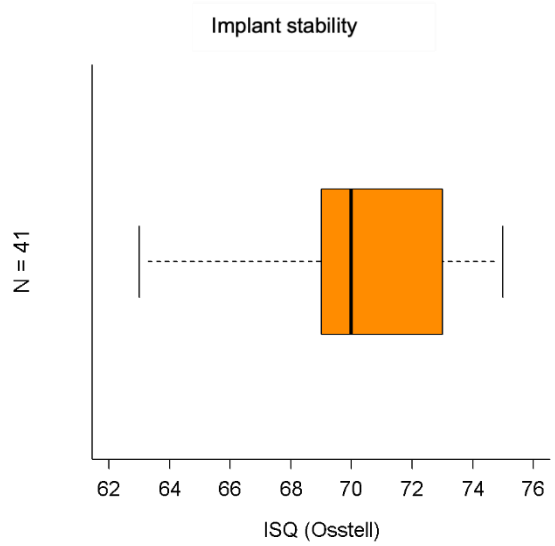

Figure 5. Distribution of implants according to stability on the Osstell ISQ scale. Box plot: extremes, minimum-maximum; edges, Q1-Q3; inner line, median.

No postoperative bleeding was reported in any of the surgeries performed. There was no mobility, suppuration or clinical mobility in any of the implants evaluated.

Discussion:

This is the first retrospective study to evaluate a protocol for dental implant placement and survival in patients with VWD. There is only one other published study including 6 patients with VWD.

Many surgical procedures in patients with coagulation disorders can be safely managed with minimal complications when properly planned and executed.

There are three treatment categories to prevent or control bleeding in patients with VWD. In less severe phenotypes, DDAVP, a derivative of Arginine-Vasopressin (a synthetic analogue of antidiuretic hormone that increases the level of FVIII and Von Willebrand Factor), can be administered intravenously or via a nasal spray. In severe cases, intravenous bolus administration of VWF or FVIII may be necessary. Finally, in some specific situations, antifibrinolytic treatments may be used. These treatments could be given together or separately depending on the type and severity of VWD[4,5].

A retrospective study by Perez-Fierro M. et al. describes a systematic protocol for placing dental implants in patients with VWD, in which type 1 patients are prepared with DDAVP, while type 2 and 3 are prepared with FVIII/FVW. However, the paper does not describe a local protocol[11]. Franchini et al. report that patients with type 1 Von Willebrand disease were given desmopressin 0.3mg/kg 1 hour before the intervention.[20] Another two case reports by Kang and Kang, and Fénelon M et al. also say that patients were systematically prepared with DDAVP and VWF, respectively, and both papers describe a local protocol. Only the case reported by Kang and Kang does not describe the use of antifibrinolytics[12,13].

Hewson ID et al. recommend careful, minimally invasive procedures, use of tranexamic acid, local hemostatic maneuvers and sutures as tight as possible when performing oral surgery in patients with type 1 and 2 VWD[21].

A retrospective study by Bogumił Lewandowski et al. reports dental extractions performed on 19 patients with hemophilia and VWD alone with systemic administration of tranexamic acid, with 3 bleeding episodes, none of which occurred in patients with VWD[22].

In the current study, only 5 of the 21 patients received prior systemic preparation with DDAVP indicated by their hematologist, and no postoperative hemorrhagic complications were reported.

No less important than the systemic preparation of the patient is the choice of both local hemostatic measures and the hemostatic agent, as these can

reduce or avoid the use of coagulation factors, which is very important from a clinical, economic and social point of view[23,24]. Many local hemostatic maneuvers have been described in the literature to control bleeding in oral surgery in patients with coagulation disorders[20,24]. Studies by Bacci et al. and Clemm et al. evaluating postoperative bleeding in anticoagulated patients undergoing dental implant placement suggest that the combined use of local maneuvers in these patients provides outcomes similar to those in patients without impaired haemostasis[25,26].

Anti-fibrinolytic therapy is a safe, low-cost treatment that prevents postoperative bleeding in patients with impaired haemostasias undergoing oral surgery[27]. The oral cavity has high fibrinolytic activity, and the use of antifibrinolytics inhibits the action of plasmin, enabling weak clots to remain intact for longer. TXA is an antifibrinolytic that can be used locally and/or systemically, not only to prevent bleeding, but also to maintain a stable clot, which is responsible for future osseointegration of implants and proper healing[28].

Several studies on implant placement in patients with coagulation disorders used and recommend antifibrinolytics[11,14,25,29,30]. A systematic review by Van Galen KPM et al. evaluating antifibrinolytic therapy to prevent bleeding in patients with hemophilia or von Willebrand's disease undergoing oral surgery found that it reduced bleeding events, amount of blood loss, and the need for other systemic therapies, without side effects[27].

Compression with gauze soaked in TXA coincides with other protocols used in different studies, including the retrospective study by Pérez-Fierro et al. in which 20 implants were placed in 6 patients with VWD. The literature recommends the use of TXA mouthwashes as a hemostatic agent. However, in agreement with Vasallo M et al., we believe that this strategy should be avoided due to the risk that the rinse may dissolve the clot[31].

In the current study, 16 of the 21 patients followed only the local protocol with local hemostatic measures and the use of topical TXA, without any systemic preparation, showing the same operative results as when combined with systemic therapy.

Flapless implant placement has succeeded in appropriately selected cases. Once the CBCT has been evaluated and it has been confirmed that there is more than 8 mm of bone in the horizontal direction, and no concavities at the apical level, a flapless approach offers a conservative alternative with minimal risk. In this technique, in which no flap is used, the approach to the bone tissue is performed with a circular scalpel, either manual or mechanized, leaving a bloody soft tissue circumference, which is very prone to generating hemorrhagic complications. When this incision is made with a circular scalpel, it is therefore recommended to use a scalpel with a smaller diameter than indicated, in order to select a healing abutment that will allow compression of the soft tissues for hemostatic purposes. This same healing abutment can be applied with a hemostatic sponge or similar product (bismuth subgallate or oxidised cellulose)[12,32]. In our work, only two flapless surgeries were performed. Nowadays, with the advance of technology, the use of precision surgical guides designed from .stl and .dicom files is recommended, which offer the possibility of using this technique with less bone tissue and, at the same time, increasingly enable surgeries to be performed with this technique[33].

Both Mathilde Fénelon and Kang and Kang have used the flapless technique, and report no postoperative bleeding complications[12,13].

In the current study, ten implants were placed immediately after extraction. None of them had hemorrhagic events, in agreement with the reports published by Fénelon and Kang and Kang. When this technique was performed, no hemostatic measures were used in addition to those used for delayed implant placement. When the calculated gap between the implant and the socket was greater than 2mm, the implant was postponed.

The current study recorded no postoperative hemorrhagic complications in the 28 surgeries performed. Perez-Fierro reports a hematoma caused

by the placement of 2 implants in a patient with VWD, which were lost after loading. Franchini et al. report only one hemorrhage in 7 patients studied[11,20].

Goldmann G et al. studied the duration of implant placement surgery in patients with inherited coagulation disorders. The median time from incision to the last stitch was 40 min in the group of patients with hereditary coagulation disorders, and 35 min in the control group. The additional time required for this meticulous surgical technique could be reflected in the longer surgery time in the group of patients with hereditary bleeding disorders. No significant differences were found in the occurrence of bleeding between the two groups. The 28 surgeries we performed took 17 to 38 minutes, with a mean of 26 minutes. It was not possible to conduct statistical analysis of the association between surgery duration and hemorrhage because no hemorrhage was recorded. This is similar to the situation reported by Vassallo M et al. in which bleeding occurred in only two cases[31,34].

Esposito M et al. in 1998 classified failures in implant dentistry in chronological order: early failure to achieve osseointegration and late failure to maintain osseointegration. This loss of osseointegration is clinically manifested by mobility. Late failures are studied to assess implant survival[35] The current study used ISQ to measure implant stability, finding a mean value of 71, which is similar to those reported in different studies evaluating implant stability[10,36].

Cochran DL et al. conducted a study in which 200 implants were evaluated at one surgical time in patients without coagulation disorders and found a survival rate of 99.4%[37]. Perez-Fierro et al. reported a survival rate of 94.6% at 2 years in the total group studied, which included patients with VWD[11]. In the current study, the survival rate was 100% according to the parameters evaluated, and ISQ values were compatible with high stability.

The decision of which brand of implants to use is based on the socio-economic condition of the patients.

Conclusions:

This is the first retrospective investigation evaluating a local and systemic hemostatic protocol for dental implant placement and survival in patients with VWD. It establishes an effective, simple, predictable treatment, mostly in patients with type 1 VWD. The survival rate and stability of the implants is similar to those reported in other studies performed on patients without disorders.

Conflict of Interest:

The authors have no conflicts of interest to declare.

Funding:

Basic Clinical Integrated Research Program of the FOUBA Res. (CD) N 330/19-01.

Acknowledgements:

None.

Ethics statement/confirmation of patients' permission:

This study was approved by the Ethics Committee of the School of Dentistry of Buenos Aires University (EXP-UBA 0040986/2019). Patient permission obtained.

References:

1. Koutts J.A short history of diagnostic tests for von Willebrand disease: in memory of Barry Firkin (1930 to 2001) and Ted Zimmerman (1937 to 1988). Semin Thromb Hemost 2006 Jul; 32 (5): 445-55.

2. Berntorp E, Peake I, Budde U, Laffan M, Montgomery R, Windyga J, et al. Willebrand's disease: a report from a meeting in the Åland islands. Haemophilia 2012 Sep;18 Suppl 6: 1-13.

3. Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, et al. Working Party on von Willebrand Disease Classification. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost 2006 Oct; 4 (10): 2103-14.

4. Nichols WL , Hultin MB , James AH , et al. Von Willebrand disease (VWD): Evidence - based diagnosis and management guidelines, the national heart, lung, and blood institute (NHLBI) expert panel report (USA) . Haemophilia 2008 ; 14 : 171 – 232 .

5. Aparna M. A medical elaboration on von Willebrand disease with its dental management. J Oral Maxillofac Surg Med Pathol 2016; 28: 442-5. [http://dx.doi.org/10.1016/j.ajoms.2016.06.005]

6. Williams M, Patel J. Von Willebrand disease: Diagnosis and management. Paediatr Child Health 2015; 25: 354-9. [http://dx.doi.org/10.1016/j.paed.2015.05.005]

7. Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, Grow JM, Kouides P, Laffan M, Lavin M, Leebeek FWG, O'Brien SH, Ozelo MC, Tosetto A, Weyand AC, James PD, Kalot MA, Husainat N, Mustafa RA. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021 Jan 12;5(1):301-325. doi: 10.1182/blood advances.2020003264. PMID: 33570647; PMCID: PMC7805326.

8. Davis A, Walsh M, McCarthy P, Brown G, Roberts S, Tran H, Street A, Fong CY, Kemp W. Tranexamic acid without prophylactic factor replacement for prevention of bleeding in hereditary bleeding disorder patients undergoing endoscopy: a pilot study. Haemophilia. 2013 Jul;19(4):583-9. doi: 10.1111/hae.12146. Epub 2013 Apr 8. PMID: 23560720.

9. Mazzeffi MA, Stone ME. Perioperative management of von Willebrand disease: A review for the anesthesiologist. J Clin Anesth 2011; 23(5): 418-26. [http://dx.doi.org/10.1016/j.jclinane.2011.02.003] [PMID: 21741810]

10. Diz P, Scully C, Sanz M. Dental implants in the medically compromised patient. J Dent 2013; 41(3): 195-206. [http://dx.doi.org/10.1016/j.jdent.2012.12.008] [PMID: 23313715]

11. Pérez-Fierro M, Castellanos-Cosano L, Hueto-Madrid JA, López-Jiménez J, Núñez-Vázquez RJ, Machuca-Portillo G. 2-years retrospective observational case-control study on survival and marginal bone loss of implants in patients with hereditary coagulopathies. Med Oral Patol Oral Cir Bucal. 2023 Nov 1;28(6):e572-e580. doi: 10.4317/ medor al.25997. PMID: 37099709; PMCID: PMC10635626.

12. Kang M, Kang P. Dental Implant Therapy on a Patient With von Willebrand Disease: A Case Study. Implant Dent. 2018 Oct;27(5):599-601. doi: 10.1097/ID.0000000000000821. PMID: 30211710.

13. Fénelon M, Castet S, Fricain JC, Catros S. Guided Implant Surgery to Reduce Morbidity in Von Willebrand Disease Patients: A Case Report. Open Dent J. 2018 Jan 31;12:80-86. doi: 10.2174 /1874210601812010080. PMID: 29492173; PMCID : PMC5815035.

14. Gatti PC, Parreira M, Gutierrez Fillol A, Gualtieri A, Puia SA. Prospective observational study on the clinical behaviour of dental implants in patients with haemophilia. Preliminary results. Br J Oral Maxillofac Surg. 2022 Feb;60(2):157-161. doi: 10.1016/j.bjoms.2021.03.014. Epub 2021 Mar 31. PMID: 34916098.

15. Sharaf B,Jandali-Rifai M, Susarla SM, et al. Do perioperative antibiotics decrease implant failure? J Oral Maxillofac Surg 2011;69:2345–50.

16. Ostman PO, Hellman M, Wendelhag I, Sennerby L. Resonance frequency analysis measurements of implants at placement surgery. Int J Prosthodont. 2006;19:77–83. [PubMed] [Google Scholar]

17. R Core Team (2023). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ .

18. Signorell A (2023). DescTools: Tools for Descriptive Statistics_. R package version 0.99.49, https://CRAN.R-project.org/package=DescTools

19. Wickham, H. (2016). ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag.

20. Franchini M, Rossetti G, Tagliaferri A, Pattacini C, Pozzoli D, Lorenz C. Dental procedures in adult patients with hereditary bleeding disorders: 10 years experience in three Italian Hemophilia Centers. Haemophilia. 2005;11:504–9.

21. Hewson ID, Daly J, Hallett KB, Liberali SA, Scott CL, Spaile G, Widmer R, Winters J. Consensus statement by hospital based dentists providing dental treatment for patients with inherited bleeding disorders. Aust Dent J. 2011 Jun;56(2):22 1-6. doi: 10.1111/j.1834-7819.2011.01328.x. PMID: 21623817.

22. Lewandowski B, Wojnar J, Brodowski R, Mucha M, Czenczek-Lewandowska E, Brzęcka D. Dental extractions in patients with mild hemophilia A and hemophilia B and von Willebrand disease without clotting factor supplementation. Pol Arch Intern Med. 2018 Aug 31;128(7-8):488-490. doi: 10.2045 2/pamw.4298. Epub 2018 Jul 11. PMID: 30057379.

23. Anderson JA, Brewer A, Creagh D, et al. Guidance on the dental management of patients with haemophilia and congenital bleeding disorders. Br Dent J. 2013; 215: 497-504.

24. Bajkin BV, Rajic NV, Vujkov SB. Dental extraction in a hemophilia patient without factor replacement therapy: a case report. J Oral Maxillofac Surg. 2012; 70: 2276-2277.

25. Bacci C, Berengo M, Favero L, et al. Safety of dental implant surgery in patients undergoing anticoagulation therapy: a prospective case–control study. Clin Oral Impl Res 2011;22:151–6.

26. Clemm R, Neukam FW, Rusche B, et al. Management of anticoagulated patients in implant therapy: a clinical comparative study. Clin Oral Impl\ Res 2016;27:1274–82.

27. 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 Dec 24;(12):CD011385. doi: 10.1002/14651858. CD011385.pub2. Update in: Cochrane Database Syst Rev. 2019 Apr 19;4:CD011385. PMID: 26704192.

28. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999 Jun;57(6):1005-32. doi: 10.2165/00003495-199957060-00017. PMID: 10400410.

29. Gornitsky M, Hammouda W, Rosen H. Rehabilitation of a hemophiliac with implants: a medical perspective and case report. J Oral Maxillofac Surg. 2005 May;63(5):592-7. doi: 10.1016/j.joms.2005.01.009. PMID: 15883931.

30. Castellanos-Cosano L, N..ez-V.zquez RJ, Segura-Egea JJ, Torres- Lagares D, Corcuera-Flores JR, Machuca-Portillo G. Protocol for oral implant rehabilitation in a hemophilic HIV-positive patient with type C hepatitis. Implant Dent. 2014 Oct;23(5):622-5. doi: 10.1097/ID.00000000000001 45. PMID:25238270.

31. Vassallo M, Zamberlin J, Roig MD, Macchi R, Aguilar JE. Efficacy of Local Hemostatic Management in Implant Surgery in Anticoagulated Patients on Warfarin: A Randomized Clinical Study. Int J Oral Maxillofac Implants. 2023 May, Jun;38(3): 545-552. doi: 10.11607/jomi.9846. PMID: 37279226.

32. Gandhi Y, Bhatavdekar N. MIDAS (Minimally Invasive Drilling And Styptic) protocol - A modified approach to treating patients under therapeutic anticoagulants. J Oral Biol Craniofac Res. 2019 Jul-Sep;9(3):208-211. doi: 10.1016/j.jobcr.2019.04.00

6. Epub 2019 Apr 30. PMID: 31193025; PMCID: PMC6514263.

33. Arisan V, Karabuda CZ, Ozdemir T. Implant surgery using bone- and mucosa-supported stereolithographic guides in totally edentulous jaws: Surgical and post-operative outcomes of computer-aided vs. standard techniques. Clin Oral Implants Res 2010; 21(9): 980-8. [PMID: 20497439]

34. Goldmann G, Berens C, Marquardt N, Reich R, Oldenburg J, Wenghoefer M. No increased bleeding risk for oral surgery in patients with severe congenital bleeding disorders due to intense perioperative management. Oral Maxillofac Surg. 2015 Jun;19(2):195-200. doi: 10.1007/s10006-014-0476-z. Epub 2014 Dec 10. PMID: 25488716.

35. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. Eur J Oral Sci. 1998 Feb;106(1): 527-51. doi: 10.1046/j.0909- 8836..t01-2-.x. PMID: 9527353.

36. Gasthi A, Rao UM, Alharethi N, Awinashe V, Sayed AJ, Parihar AS, Manas A. Comparative Evaluation of Two Implant Designs Based on Bone Loss and Stability with Early Loading Method. J Pharm Bioallied Sci. 2023 Jul;15(Suppl 2):S885-S887. doi: 10.4103/jpbs.jpbs_84_23. Epub 2023 Apr 28. PMID: 37694065; PMCID: PMC10485410.

37. Cochran DL, Jackson JM, Jones AA, Jones JD, Kaiser DA, Taylor TD, Weber HP, Higginbottom FL, Richardson JR, Oates T. A 5-year prospective multicenter clinical trial of non-submerged dental implants with a titanium plasma-sprayed surface in 200 patients. J Periodontol. 2011 Jul;82(7):990-9. doi: 10.1902/jop.2011.100464. Epub 2011 Jan 14. PMID: 21235337.

