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Article

Management of Patients with Coagulation Disorders Undergoing Minor Oral Surgery.

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Abstract: Objective: The purpose of the present study was to analyze the management of dental extractions in patients affected by coagulation disorders in order to prevent bleeding intraoperative and postoperative complications. **Subjects and Methods:** This study included 17 patients with a diagnosis of a coagulation disorder, who had been subjected to a single or multiple dental extraction. Recombinant activated Factor VII was administered in those patients who were affected by a deficit of factor VII ranged between 10,5% and 21%. The other patients were treated locally with tranexamic acid. **Results:** A total of 50 teeth were extracted, 7 by surgical extraction and 43 by simple extraction. Of the 17 patients included 9 of them suffering from factor VII deficiency, 5 from factor V deficiency, 1 from Glanzmann's thrombasthenia and 2 from Haemophilia A. Pretreatment with recombinant activated factor VII was performed on a total of 8 patients with factor VII deficiency; the remaining 9 patients underwent tranexamic acid treatment. 1 hemorragic postoperative complication was observed. **Conclusions:** Surgical and no surgical extractions appear to be a safe procedure for patients affected by coagulation disorders when appropriate prophylaxis is adopted.

Keywords: Mouth; Dental diseases; Surgery

1. Introduction

T Patients affected by coagulation disorders are at high risk of intra- and postoperative bleeding complications when oral surgery procedure has to be performed. Therefore management of patients with coagulation deficit requires cooperation between oral surgeons and haematologists. [1]Haemophilia A is a hereditary X-linked recessive chromosomal bleeding disorder. Approximately 1:5,000 males are affected. It's caused by a moltitude of mutations of the factor VIII gene, only men are expressing the disease, meanwhile women are asymptomatic carriers. In fact most cases have a prior family history of Haemophilia A. We can classify Haemophilia A in: mild when plasma activity is between 6 and 40 % of normal; moderate if it ranges between 1-5 % and severe if it is <1 %. [2, 3]Glanzmann's thrombasthenia (GT) is a rare autosomal recessive bleeding disorder that is characterized by a quantitative or qualitative defect of glycoprotein IIb/IIIa (GPIIb/IIIa) on the platelet membrane, which is a receptor for fibrinogen. As a result, no fibrinogen bridging of platelets to other platelets can occur, and the bleeding time is significantly prolonged. [4] The deficit of FVII, also known as serum prothrombin conversion accelerator deficiency or Alexander's disease, is a rare (1/500.000) autosomal recessive disorder caused by mutations of the gene F7. A severe deficiency is expressed in homozygous individuals, meanwhile heterozygous are affected by a moderate one. [5, 6] The Factor V deficiency, also called Owren's disease, is a rare (1/1.000.000) autosomal recessive disorder, it

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affects men and women equally. Common symptoms are: bruising, nose and mouth bleeding, prolonged bleeding after trauma or surgery and spontaneous bleeding under the skin. In severely affected individuals it can cause intracranial, gastrointestinal and pulmonary hemorrhage. In oral surgery the use of coagulation factor replacement therapy is required. [7, 8, 9] Successful treatment protocols are described in the current literature using systemic treatment, antifibrinolytic agents and local haemostatic measures. [10] Recombinant activated factor VII is indicated for the treatment of intraoperative and postoperative bleeding in patients with a diagnosis of Haemophilia A, Glanzmann Thromboasthenia and congenital FVII deficiency. [4, 11] For patients affected by FV deficiency a specific concentrate is not available, so the most indicated treatment is fresh frozen plasma (FFP) intravenously injection. In alternative are also indicated platelet concentrates, recombinant activated factor VII and tranexamic acid. The purpose of the present study was to analyze the management of multiple dental extractions in patients affected by the following coagulation disorders: Factor VII deficit, Haemophilia A and Glanzmann thrombasthenia, in order to prevent bleeding intraoperative and postoperative complications. [4,6] 2. Materials and Methods

The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

2. Materials and Methods

The present retrospective study included 17 patients (6 men and 11 woman) affected by Factor VII deficit, Factor V deficit, Haemophilia A and Glanzmann thrombasthenia, aged 19 to 78 years, who had undergone single and multiple dental extractions (Table 1) at the Oral Surgery Unit, Policlinico Universitario Agostino Gemelli (Rome, Italy) from 10/2013 to 10/2018. Because of the retrospective nature of the present study, it was granted an exemption in writing by the institutional review board of the Catholic University of the Sacred Heart of Rome.We have read the Declaration of Helsinki and followed the guidelines in the present investigation. Ethical approval was obtained from the Catholic University of Sacred Heart, Rome, with the ethics committee protocol number 23236/17, ID1608. The data were obtained by analyzing the clinical records and the haematological examinations of the patients included in the study. The latter fell within the ASA classification (American society of Anesthesiologists) as class 1 or class 2 patients. A preoperative panoramic radiography was performed and reviewed for each patient. Each tooth was extracted with a lever and extraction forcep under local anesthesia, performed using 2% mepivacaine with 1:100.00 epinephrine. The surgical protocol varied according to the difficulty of extraction, therefore we have adopted a surgical extraction protocol (which includes flap lifting, osteotomy and odontotomy) to perform extractions of impacted teeth and fractured roots. A bone curette and physiologic saline were used to clean and wash the alveolar socket immediately after the extraction. Packing the alveolar socket with a gelatin sponge (SPONGOSTAN; Ferrosan Medical Devices A/S, Søborg, Denmark) helped to obtain local hemostasis. Then 3.0 silk was used to suture the site in order to obtain a

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primary closure and less postoperative disorders. Postoperative instructions including local ice packs applications and semiliquid diet for the first day were also given to the patients. The patients were observed for a period of 4 hours after the dental extraction. Before the extraction, the patients affected by Glanzmann's thrombasthenia, Factor V deficiency, Haemophilia A and low grade FVII deficiency rinsed their mouth with 10 mL of tranexamic acid for a period of 10 minutes. After the extraction, the patients were instructed to rinse their mouth with 10 mL of tranexamic acid for 10 minutes every 6 hours for the first day. [12] rFVIIa (NovoSeven RT; Novo Nordisk) was transfused intravenously in a single dose of 25 mg/kg body weight, 30 minutes before surgical extraction to patients affected by FVII deficit, who had an impact tooth, so we had to adopt the surgical protocol. During the 7 days following the extraction all patients were monitored, recording any eventual bleeding, pain and swelling. A swelling and bleeding scale has been drawn up with scores from 0 to 3: score 0, which represents the absence of the aforementioned episodes; score 1: mild; score 2: moderate; score 3: serious. Pain was assessed by means of the visual analogue scale (VAS), with limitations from 1 to 10, with 1 to 2 indicating a very mild and mild pain and from 9 to 10 indicative of intolerable and excruciating pain.

PT. NO	AGE (YR)	SEX	TEETH EXTRACTED (N)	COAGULATION DISEASE	SURGICAL EXTRACTION
1	23	F	1	FVII deficiency	1
2	31	F	1	FVII deficiency	1
3	24	M	1	FVII deficiency	1
4	19	F	1	FVII deficiency	1
5	28	M	1	FVII deficiency	1
6	19	F	1	FVII deficiency	1
7	23	F	1	FVII deficiency	1
8	36	F	3	FV deficiency	0
9	39	F	3	FV deficiency	0
10	55	F	12	FV deficiency	0
11	73	F	6	FV deficiency	0
12	45	F	1	FV deficiency	0
13	54	M	3	Glanzmann's thrombasthenia	0
14	58	M	3	Haemophilia A	0
15	26	F	4	FVII deficiency	0
16	78	M	3	Haemophilia A	0
17	53	M	5	FVII deficiency	0

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3. Results

The laboratory findings from the 17 patients with coagulation disorders are listed in **Table 2**. The mean PT and aPTT were 17.24 seconds and 35.46 respectively. The mean INR at diagnosis was 1.88. All the subjects underwent at least 1 tooth extraction. A total of 50 teeth were extracted, 7 by surgical extraction and 43 by simple extraction. 17 patients were included in the present study, 9 of them suffering from FVII deficiency, 5 from FV deficiency, 1 from Glanzmann's thrombasthenia and 2 from Haemophilia A. Pretreatment with recombinant activated factor VII was performed on a total of 8 patients with FVII deficiency; the remaining 9 patients underwent tranexamic acid treatment. 1 hemorragic postoperative complication was observed in a patient affected by FVII deficiency in the present study .All the extraction sites showed excellent healing at suture removal 7 days postoperatively and at 2 weeks and 1 month postoperatively.

PT NO.	PT(SECONDS)	INR	APTT(SECONDS)	FII(%)	FV(%)	FVII(%)	FVIII(%)	FX(%)
1	15.3	1.4	33.1	120.2	143.5	14.0	100.5	93.0
2	14.5	1.8	35.2	115.0	140.2	10.5	97.0	102.7
3	19.7	2.0	25.4	105.0	127.4	11.2	88.3	110.3
4	14.9	1.3	26.7	118.5	139.0	13.5	99.4	98.0
5	19.6	1.9	25.2	98.0	110.4	17.7	112.3	115.6
6	17.4	1.5	25.5	102.7	108.9	21.0	105.0	95.5
7	18.2	2.0	26.1	120.3	105.6	12.3	102.1	130.0
8	16.1	1.8	42.3	112.4	14.1	78.0	75.2	86.8
9	15.6	2.2	39.8	97.0	15.4	100.6	92.7	111.8
10	18.7	1.9	44.5	120.7	20.0	110.2	98.9	118.1
11	13.9	1.6	40.8	110.3	22.4	98.6	81.6	96.7
12	20.1	1.8	45.6	96.0	18.9	91.4	100.2	89.9
13	19.7	2.0	24.4	98.3	100.2	90.0	89.5	92.8
14	18.2	1.7	44.3	108.4	109.9	100.1	104.6	94.1
15	20.0	1.9	40.2	105.2	137.4	36.0	111.2	97.5
16	16.5	2.2	38.7	100.3	106.5	102.2	107.8	106.8
17	14.7	2.0	43.1	99.7	108.6	33.2	99.8	100.3

4. Discussion

Intraoperative severe bleeding during an oral surgery procedure is a complication that besides putting at risk the general health of the patient does not allow the surgeon to operate in ideal conditions, and this is precisely the reason why the correct management of patients with coagulation disorders is so important. Close cooperation between surgeon and haematologist could be of great help in establishing a protocol of prophylaxis in order to prevent massive local bleeding during and after surgery. Failure or erroneous management of patients with coagulation disorders could lead to prolonged bleeding of the site, which could put the patient's life at risk, especially in the postoperative setting. [13, 14] The use of rFVIIa has been shown to prevent severe bleeding in patients with FVII deficiency who have undergone surgical extractions. The collaboration with the hematologist in this case is important in order to prescribe a correct dosage and a correct frequency of

intake, which varies for each patient based on the level of hereditary deficiency of FVII, which directly influences the risk hemorrhagic; at the duration and level of extension of the surgical procedure; at the infectious risk; to the patient's symptoms related to FVII deficiency. The hemorrhagic risk for these patients is considered very high when there are plasma concentrations of FVII lower than 1%, high if they are between 1% and 10%, medium if they are between 10% and 25%, and low if they are less than 25%. [6, 15] For patients with other coagulation disorders for which a specific substitute is not available as for FVII deficiency, we have adopted a protocol based on antifibrinolytic agents such as tranexamic acid since its effectiveness in decreasing bleeding has been proven intra and post operative, and above all because it can be administered orally, intravenously and as a mouthwash. By adopting a protocol combined with tranexamic acid, placing a fibrin sponge inside the alveolus and closing by primary intention by means of non-resorbable intraoral sutures, we were able to achieve excellent postoperative bleeding control and minimize complications. The most important advantages of this therapy are the fact that it does not subject the patient to a systemic therapy, so it is easier to administer and above all it is cheaper. Obviously each case should be evaluated individually, and in case of reduced experience of the operator, even for these patients it is recommended a close collaboration with the hematologist. Although having used a prophylactic antifibrinolytic protocol, in our study we found a case of abundant postoperative bleeding, in a patient suffering from mild FVII deficiency, we believe this to be attributable to the fact that 2 extractions of high complexity were performed during the same session. We treated the patient by performing plasma transfusions. Consequently, we always recommend to be cautious even in cases that apparently can seem low risk, and therefore always perform an extraction procedure at a time, as we did for the next 3 teeth, without finding any complication.

5. Conclusions

Surgical and no surgical extractions appear to be a safe procedure for patients affected by coagulation disorders when appropriate prophylaxis is adopted.

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