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Research Article

Perioperative Management of Patients with Rare Congenital Factor Deficiency

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Abstract

Objectives: Fibrinogen, prothrombin, factor V, VII, X, XI, XIII and V+VIII deficiencies are defined as rare congenital factor deficiencies (RCD). Due to small number of patients and lack of data, perioperative management can be challeging. We aimed to evaluate the RCD patients who underwent surgery.

Methods: Thirteen women, eight men, totally 21 patients was retrospectively analyzed.

Results: Ten patients were diagnosed incidentally by investigating the bleeding tests performed before the procedure and routine bleeding tests. Two patients had diagnosed with fibrinogen disorder, one patient factor V deficiency, 9 patients factor VII deficiency, 2 patients factor X deficiency, 4 patients factor XI deficiency, 3 patients combined factor deficiency. Six patients underwent gynecological intervention, 4 patients dental procedures, 2 patients orthopedic surgery, 2 patients appendectomy, 2 patients urological intervention, one patient gastrectomy, one patient rhinoplasty, one retinal surgery, one lipoma excision, one cardiological intervention. Two of the patients were treated with only antifibrinolytic therapy before the procedure/surgery, while 19 patients were treated with replacement therapy appropriate to their disease. Ten patients were continued with replacement therapy after the procedure/surgery. None of the patients had bleeding.

Conclusion: Perioperative management of patients with rare factor deficiency is crucial in terms of bleeding and related complications.

Keywords: Bleeding, Bleeding disorder, Blood coagulation disorders, Factor deficiency, Surgery

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Rare congenital factor deficiencies, also known as rare coagulation disorders (RCD) in the literature, are diseases that account for about 2-5% of all congenital bleeding disorders, including coagulation disorder diseases other than hemophilia A and B.[1] Factor I (fibrinogen), factor II (prothrombin), factor V, factor V+VIII, factor VII, factor X, factor XI, factor XIII deficiencies are named as inherited rare factor deficiencies. The inheritance is autosomal recessive except for the autosomal dominant inheritance of dysfibrinogenemia and some factor XI deficiencies.[1-3] Factor VII deciency is the most common RCD and its frequency has been reported 1/500 000 people.[1] Due to its autosomal recessive inheritance, its prevalence may increase in countries where inbreeding or consanguineous marriage is frequent, such as our country.[1, 2, 4, 5] In RCD cases, which the clinical bleeding symptoms are quite different from patient to patient, patients may have a wide range of clinical features, ranging from asymptomatic clinic to life-threatening bleeding. Fibrinogen, factor X, factor XIII deficiencies had been found to correlate with factor levels in terms of bleed-

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ing symptoms, while there is no correlation for factor factor V, V+VIII, VII and XI deficiencies.[1, 3, 6] Although the bleeding spectrum of RCD patients also differs in terms of the bleeding location, bleeding can often be observed in nearly all of the patients from mucosal tissues and during/ after invasive procedures. Surgical/interventional procedures and management of RCD patients are not as definite as hemophilia A and B patients. The information on this subject comes from the case reports, case series and reviews of these publications.[7-11] Based on this information, as it is important to the know about the diagnosis, follow-up and treatment processes of RCD patients, we aimed to analyze RCD patients, which is rare but can be challenging when the patients have bleeding during or after surgeries and interventions, in our tertiary center.

Methods

Twenty one patients who were followed up with the diagnosis of RCD and underwent interventional procedures at our center between years 2019 and 2023. The data of the patients was analyzed retrospectively. The patients' diagnoses, ages, ages at diagnosis, diagnostic bleeding information, family history, basal coagulation test results, type of the intervention or surgery, treatment given before the intervention/surgery, bleeding information during or after the interventions, treatment after procedures were recorded.

Ethical approval for the study was obtained from the ethics committee of our center with the number E1-22-2411.

Statistical analyses were performed by using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics were presented as n and % for categorical variables, mean and median for continuous variables.

Results

In the study, 13 female and 8 male patients were evaluated. The median age of the patients was 37 (22-88). The median age at diagnosis was 8 (0-83). Five of the patients (24%) had inbreeding marriage in their family and 4 patients had a family history of a RCD person. The diagnostic subtypes of the patients is shown in Figure 1. Two of the patients were diagnosed with umbilical cord bleeding after childbirth, 4 of them were diagnosed due to mucosal bleeding, 4 of them were diagnosed due to gynecological bleeding, 1 of them was diagnosed due to bleeding after tooth extraction. One of the patients diagnosed with umbilical cord bleeding immediately after birth was afibrinogenemia and the other patient was with factor X deficiency.

Ten patients were diagnosed with rare factor deficiency by investigating the detection of a disorder in the bleeding

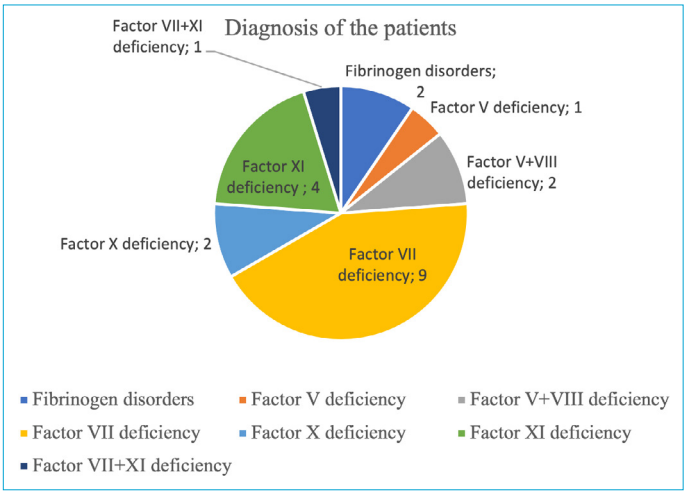

Figure 1. Diagnostic subtypes of the patients.

tests examined before the intervention without any bleeding history. Six of these ten patients had factor VII, two patients had factor XI, one patient had factor V+VIII, one patient had factor VII+XI deficiency.

The range activated partial thromboplastin time (aPTT) of patients with intrinsic coagulation pathway disorder or deficiency of factors affecting the common coagulation pathway was between 34 seconds and 118 seconds (normal range of the laboratory was 21-32 second), and the median was 53.5 seconds. For patients with a deficiency of factors affecting the extrinsic coagülation pathway or common coagulation pathway, the prothrombin time (PT) was median 20.1 seconds with a changing value between 11.3 and 46.6 seconds (normal range of the laboratory was 9.8-14 second). Only one of the patients had normal PT and this patient had factor VII deficiency. The baseline factor levels of the patients were median 4% (0.9-27). The measurable level was 0.3 g/L in patients with fibrinogen disorder. Only the afibrinogenemia patient was receiving prophylaxis treatment. The history of joint bleeding had been observed in afibrinogenemia patient and factor X deficiency, and these patients had no permanent arthropathic sequelae.

Six patients underwent gynecological intervention, 4 patients dental procedures, 2 patients orthopedic surgery, 2 patients appendectomy, 2 patients urological intervention, one patient gastrectomy, one patient rhinoplasty, one retinal surgery, one lipoma excision, one cardiological intervention. Two of the patients were treated with only antifibrinolytic therapy before the procedure/surgery, while 19 patients were treated with replacement therapy appropriate to their disease. Ten patients were continued with replacement therapy after the procedure/surgery. The interventions-surgeries, the treatments given before the procedure, the bleeding status during and after proce-

dures were presented in Table 1. None of the patients had bleeding during the interventions. No bleeding-related morbidity or mortality was observed in any patient during follow-up. There were no thromboses or wound healing problems in any patient.

Conclusion

RCDs are factor deficiencies other than factor VIII and factor IX deficiency. The prevelance of RCDs varies from one in 500 thousand to one in 2 million people. Bleeding spectrum of the patients vary from asymptomatic clinic to fatal bleedings. In addition to the subtypes diagnosed with umbilical cord bleeding, there may also be patients who have not expericience bleeding for their whole lifetime without receiving a diagnosis.[1,5, 12] Although the most common side of bleeding is mucosal, bleeding after the intervention is also common in RCD patients . Due to their rarity, there is a lack of clinical research and epidemiological data about these diseases. In addition, many subtypes of clinical bleeding conditions are not correlated with the basal factor level.[1, 6, 13] Although there are some recommendations for these patients about the procedures before the interventions, there are no guidelines from large general patient data, such as in hemophilia A and B. For these diseases, in which the diagnosis-treatment process, prognostic information had been reported with case series and review data, we also want to show the data of our patients with RCD who underwent a surgical intervention.

The diagnostic distribution of patients in our study was similar to a study conducted in Iran, with frequent inbreeding country and studies from our country.[2, 5, 11, 14] Factor VII deficiency was the most common subtype.

Since family and patient's bleeding history had an important point in the diagnosis, prediction of the patient's clinical bleeding symptoms and in the individualized approach in the treatment process, these data had been included in our study. Ten of the 21 patients were diagnosed at an adult age and based on routine or pre-intervention coagulation tests. This was compatible with the informationa of RCDs commonly asymtomatic clinic.[1, 2, 13] Also, the presence of umbilical cord bleeding in two patients is an indicator of presentation in the newborn in some subtypes and with a serious bleeding symptom in accordance with the literature information.[11, 13] The information that four of 11 patients with a history of bleeding had mucosal bleeding and 4 had gynecological bleeding is also consistent with the

Table 1. Demographical data, surgical informations, replacement treatments of the patients

Patient number	Diagnosis	Age	Factor Level	Surgery/Intervention procedure	Treatment before procedure	Treatment after procedure
1	Dysfibrinogenemia	48	0,3 g/L	Lipoma excision	Fibrinogen concentrate	No
2	Afibrinogenemia	22	0,3 g/L	Shoulder joint operation	Fibrinogen concentrate	Yes
3	Factor V deficiency	30	2%	C/S	FFP	Yes
4	Factor V+VIII deficiency	39	8/12%	Tooth extraction	FFP	No
5	Factor V+VIII deficiency	35	11/12%	C/S	FFP+factor VIII concentrate	Yes
6	Factor VII deficiency	50	4%	Tooth extraction	rFVIIa	No
7	Factor VII deficiency	68	2%	Cystoscopic bladder resection	rFVIIa	Yes
8	Factor VII deficiency	27	6.8%	Rhinoplasty	rFVIIa	Yes
9	Factor VII deficiency	88	18%	Gastrectomy	rFVIIa	Yes
10	Factor VII deficiency	37	25%	Vaginal delivery	Tranexamic acid	No
11	Factor VII deficiency	46	25%	C/S	Tranexamic acid	No
12	Factor VII deficiency	34	3%	Orthopedic fracture surgery	rFVIIa	Yes
13	Factor VII deficiency	25	27%	Laparotomic ovarian cyst surgery	rFVIIa	Yes
14	Factor VII deficiency	20	15%	Appendectomy	rFVIIa	Yes
15	Factor X deficiency	44	1.9%	Appendectomy	PCC	Yes
16	Factor X deficiency	24	1%	Tooth extraction	PCC	No
17	Factor XI deficiency	24	0.9%	C/S	FFP	No
18	Factor XI deficiency	84	2%	Cystoscopic bladder resection	FFP	No
19	Factor XI deficiency	20	2%	Retinal surgery	FFP	No
20	Factor XI deficiency	70	2%	Tooth extraction	FFP	No
21	Factor VII+XI deficiency	52	0.9/2.4%	TAVI	FFP	No

C/S: Cesarean section; FFP: Fresh frozen plasman; rFVIIa: Recombinant factor VIIa; PCC: Prothrombine complex concentrate; TAVI: Transcatheter aortic valve implantation.

dominance of mucosal bleeding in patients with according to the literature.[2, 15]

Fibrinogen concentrate, which is especially recommended before the intervention in all over the world for afibrinogenemia/dysfibrinogenemia patients, is also available for use in our country.[6, 7, 16] Other recommended replacement therapy options for these patients are fresh frozen plasma (FFP) and cryoprecipitate.[12, 16] Fibrinogen concentrate named "Haemocomplettan" is available in our country. Two of our patients with fibrinogen disorders were treated with this fibrinogen concentrate before the intervention. The patient who underwent minor surgery with lipoma excision was treated with "Haemocomplettan" before surgery and the target fibrinogen level was calculated to be 1 g/L before the procedure. Calculation was made with the formula

$$\frac{[\text{Target fibrinogen level-baseline level (mg/dl)}] \times \text{body weight (kg)}}{1.7}$$

Due to the fact that it was a minor surgery and the fibrinogen half-life was 3-4 days, no additional dose was administered. There was no bleeding or thrombosis in the patient. Fibrinogen concentrate was given to the other fibrinogen disorder patient according to the same formula with a target fibrinogen level of 1.5 g/L, since our second patient had undergone a major surgery for shoulder joint operation. According to the literature, for a good wound healing and bleeding control replacement therapy is recommended with a target level of 1 g/L fibrinogen for 4-14 days after major surgery.[7, 16, 17] Therapy with fibrinogen concentrate was continued with a second dosage 3 days later after the first administration in our patient with a target fibrinogen level of 1 g/L for wound healing after major surgery. The patient did not have bleeding, thrombosis or wound healing problems.

There was a previous history of postpartum bleeding and severe deficiency in our patient with factor V deficiency. Tranexamic acid 15 mg/kg was given every 6 hours for 3 days starting before delivery by planned cesarean section. FFP was given 30 minutes before section and continued with the dosage 10 ml/kg, every 12 hours for 3 days in accordance with the recommendation of the literature.[6, 16, 17] There was no bleeding, thrombosis, wound healing problems.

Replacement therapy is recommended to be performed with FFP which contains both factors in case of factor V+VIII combined deficiency.[6, 16, 17] The half-life of factor V is 16-36 hours and the half-life of FVIII is 10-14 hours. Although concentrates are available for factor VIII; factor V replacement treatment should be performed with FFP, since there is no concentrate for factor V.[16, 17] FFP' s factor V and VIII content is about 0.7-0.9 IU/ml and since the dosing frequency will not match during maintenance due to the shorter half-life of factor VIII, the use of desmopressin and factor VIII concentrate is recommended as a source of factor VIII.[6, 16] There is no factor V in cryoprecipitate, so it is not an appropriate replacement therapy for factor V and VIII combined deficiency. For low-risk minor surgeries, only antifibrinolytic therapy can be adequate.[6, 16] A single dosage of 15 ml/kg FFP was given to our patient who had undergone a molar tooth extraction with a previous clinical bleeding history. No complications developed in the follow-up. C/S operation was planned for the patient with the second combined factor deficiency. The factor levels examined before the operation were 11% and 12%, respectively. In addition to FFP replacement before the operation, the patient was given factor eight concentrate, as the factor eight level could be elevated during pregnancy. Due to the recommendation of factor replacement continuation in the wound healing process for combined deficiencies, the patient was given an additional dose of FFP and factor eight concentrate 12 hours after postoperation.[16] While FFP is recommended to be given every 12 hours for at least 3 days in patients with severe deficiency of factor V level in the third trimester, only one additional dose of FFP was given to our patient, since the factor V level was 11% in our patient and the level was not expected to change during pregnancy.[16]

Factor VII has a half-life of 4-5 hours. In case of deficiency, it is recommended to apply recombinant factor VIIa (rFVIIa) at a dose of 15-30 mcg/kg immediately before the operation, depending on the operation procedure, a second dosage should be applied 12-24 hours later, and then a decision has to be made to apply the factor for 1-3 days depending on the bleeding condition and the patient.[6, 16-18] Seven patients with factor VII deficiency who underwent surgery were given rFVIIa at a dose of 15 mcg/kg preoperatively with tranexamic acid in accordance with surgery, and for six patients additional replacement therapy was administered up to 3 days postoperatively in accordance with major surgery and bleeding monitoring. Two patients who underwent two gynecological interventions were taken to the surgery only with tranexamic acid therapy. No complications were observed during the follow-up.

The replacement option for our factor X deficiency patients is FFP or prothrombin complex concentrates since only factor X-containing concentrates approved in some countries have not yet entered into usage in our country. Prothrombin complex concentrates contain factor X, as well as factor II, VII and IX, and it is recommended to carefully calculate the dosage, since the levels of factor X in content of preparations are different.[12] The use of activated prothrombin complex is not recommended due to the risk of throm-

boembolism.[17] For patients with FX deficiency, a loading dose of 15- 20 IU/kg before surgery and a daily dose of 10-15 IU/kg after surgery, or even every two days in minor surgeries is sufficient.[17] In one of our cases, a patient with severe factor deficiency was given a prothrombin complex concentrate of 20 IU/kg with tranexamic acid before tooth extraction. In our other patient, the basal factor level was 1.9% and the patient was given 20 IU/kg prothrombin complex concentrate before appendectomy, postoperative 15 IU/kg of prothrombin complex concentrate was given in postoperative first day. In our country, a PCC preparation containing four factors is in use, and the dose calculation was made according to the factor X level in the product. No complications were observed in both patients during the follow-up.

FFP, FXI concentrate or rFVIIa can be used before the intervention for factor XI deficiency patients.[16, 17] The half-life of FXI is 46-52 hours. There is no single factor XI concentrate available in our country. It is not recommended to use antifibrinolytic agent together with FXI concentrate in the first 24 hours because it increases the risk of thrombosis.[6, 16] A single dosage of FFP of 15 ml/kg was administered to our patient with four factor XI deficiency before the retinal surgery, cystoscopic bladder resection, cesarean delivery and tooth extraction. Patients who underwent cesarean delivery and dental procedure also received tranexamic acid treatment. No bleeding was observed during the follow-up.

There is a limited number of reported cases of factor VII+XI deficiency in the literature.[19-21] Our patient who was diagnosed with factor VII+XI deficiency preoperatively at the age of 51 when he was investigated due to preoperative aPTT and PT prolongation. He was planned to underwent a transcatheter aortic valve implantation. The patient had a baseline factor XI level of 0.9% and a factor VII level of 2.4%. He was given 20 ml/kg FFP before intervention. There was no complication.

As a result, no complications were observed in our RCD patients who had underwent surgical procedures with appropriate replacement and supportive treatments. The management of surgical procedures of patients with rare factor deficiency is important in terms of bleeding in the post-surgical period. For this reason, it is crucial for these patients to perform procedures/surgeries safely in experienced centers with appropriate blood product replacement and supportive therapies in accordance with recommendations with a multidisciplinary approach.

Disclosures

Ethics Committee Approval: Ethical approval for the study was obtained from the ethics committee of our center with the number E1-22-2411.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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