International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Random Use of Recombinant Activated Factor VII in Pediatric Age Groups

Aisha. M. Al-Doroobi [1], Hayat. H. Obayid [2], Khalid. B- Kago[3]

[1](M.B.Ch.B-DCH) Head of Neonatal Unit/Ibn Al-Balady hospital Head of Neonatal Unit/Ibn Al-Balady hospital. Pediatrician/ Ibn Al-Balady Hospital for Children

[2] (M.B.Ch.B-DCH) Head of Neonatal Unit/Ibn Al-Balady hospital Head of Neonatal Unit/Ibn Al-Balady hospital. Pediatrician/ Ibn Al-Balady Hospital for Children

[3](M.B.Ch.B-DCH) Head of Neonatal Unit/Ibn Al-Balady hospital Head of Neonatal Unit/Ibn Al-Balady hospital Pediatrician/ Ibn Al-Balady Hospital for Children

Abstract: ***Bleeding disorders in pediatrics is an important issue and can be life threatening if not diagnosed and treated appropriately. Infants and their families who are affected by these illnesses have poor life quality and often dysfunctional. In this study, we focused on bleeding disorders that have high prevalence in infants and children and are often over looked in other trials and studies where most of their focus was dedicated towards using factor VII in pre-andpost-operative hemorrhages and trauma. We involved 35 patients with various bleedings disorders whom were treated with recombinant factor VII with follow-up over the course of six months. The drug proved its effectiveness with success rate as high as 91.4% and mortality rate of 8.5%.***

Keywords: Recombinant, Factor VII, Bleeding disorders, Hemorrhage, pediatrics, Hematemesis

1. Introduction

Bleeding disorders are a life threatening problems in all age groups and present a challenge in medical practice all over the world. Consequently, the first priority is to stop the bleeding and provide Heamostasis with minimal use of additional adjuvant therapy. One of the most promising drug is the (Recombinant Factor Seven - RFVIIa). This Medicine was first used in (1970) in the treatment of blood disorders with low Thromboembolic side effects. After that, it was used in treatment of Heamophelia, Congenital Fator VII deficiency, "Glanzmann's Thrombosthenia [1]. RFVIIa had also been used in treatment of pulmonary heamorrhage and in very low birth weight infants (Premature) [2], DIG [3], liver disease, G.I.T. bleeding, Intracranial Heamorrage and NEC [4]. RFVIIa was used also in pediatric patients with acute Idiopathic Thrombocyto Pania presented with Heamafuria [5].

In this prospective study, RFVIIa was used in children with life threatening bleedings because of its safety and efficacy. The safety of RFVIIa is due to its recombinant nature and to the site of its action on the activated platelets at site of injury only [6] and there is no systematic activation of coagulation, hence, there will be low risk of Thromboembolic phenomenon [4].

The use of RFVIIa must be weighed against implications and costs. The cost differ in different countries, but it is about (1.5 US$) in general for each microgram of the drug [7].

2. Aim of the Study

The aim of our study is to stop bleeding and treat bleeding disorders which are life threatening. Another goal is to decrease the use of adjuvant therapy as frozen plasma, packed cells and vitamin K. RFVIIa was also used pre- and post-operatively to decrease bleeding in normal and Heamophilia patients by by-passing the inhibitors and provide Heamostasis.

3. Methods and Materials

3.1 Patients Data

This perspective study was done at (IBN ALBALADI Hospital for Children and Maternity) between (May to December - 2018). It involved (35) patients at different age group and gender. Patients were divided into two groups; "Control Group" consisting of (16) patients, and "Study Group" consisting of (19) patients. Both groups were given RFVIIa to control their bleeding. They have been followed-up for (6) months after the treatment to observe and detect side effects of the drug such as Thromboembolism.

3.2 Tests

The tests used are; Complete Blood Picture (CBC), Blood Film, Prothrombin Time (P.T.), Partial Thrombin Time (P.T.T), Blood Culture, and sensitivity. These tests were done before and after the therapy with RFVIIa.

3.3 Dosage

RFVIIa was used in dose of 90 ug\kg in all the patients (except for one time when 40 |J.g\kg was used). Some of them were given single dose and responded with bleeding stopped, others needed multiple doses for few days to respond. Some patients needed adjuvant therapy such as plasma, vitamin K or packed cells transfusion, while other patients did not need additive therapy depending on diagnosis and type of bleeding. RFVIIa was given by

intravenous transfusion slowly and under close medical supervision over period of (30) minutes.

4. Results and Analysis

In the control group, (16) patients were treated with RFVIIa, they responded quickly and bleeding stopped. They were all discharged well from the hospital except for one patient who was of (5) years of age and was diagnosed with Liver Cirrhosis and oesophageal varices. He received RFVIIa as a single dose in addition to one pint of fresh frozen plasma and was referred for surgical treatment after cessation of bleeding, he died during surgery. The efficacy was (93.75%), and death rate was (6.25%) in this control group.

In study group, (2) patients died because they were presented late in the disease when the platelets count was below (150 000 x 109), so it is important to start the treatment as soon as possible. In study group, (17) patients responded to treatment with RFVIIa and were discharged home well. The efficacy was (89.4%) and death rate was (10.5%). No side effects had been observed in either group such as Thromboembolic phenomenon. Follow-up for six months duration after treatment with RFVIIa was performed.

The dose of RFVIIa used in our study was (90 ug/kg/dose) in all the patients except in one, where (40 ug/kg/dose) was used because of shortage and unavailability of the drug. In the control group, (13) patients (81.25%) received single dose and bleeding stopped, while in (3) patients (18.75%) received multiple doses (every 8 hours) for (2-3) days until they responded due to the severity of the bleeding. Only (3) patients (-18.75%) of the control group received adjuvant therapy as fresh frozen plasma packed RBC. While the rest (~81.25%), were given only RFVIIa as the only dry therapy.

In the study group (8) patients (42.1%) needed single dose of RFVIIa, while the other (10) patients (57.8%) needed multiple doses (every 8 hours) for (2-4 days). All the study group treated with RFVIIa in dose of (90 ug/kg/dose). The need for adjuvant therapy as fresh frozen platelets, packed cells and vitamin K were reported to be used on (4) patients (26.6%), while the rest of the patients (73.3%) did not need adjuvant therapy. The efficacy rate as a whole was (91.4%), while the mortality rate as a whole was (8.5%)

Table 1: Control group patients

No.	Age (y)	Weight (kg)	Gender	Presentation	Diagnosis
1	1	10	m	gum bleeding	Von-Willbrand disease
2	2	9.4	f	rectal bleeding	Von-Willbrand disease
3	3	15	m	epistaxis	heamophelia
4	0.75	8.8	m	malena	Von-Willbrand disease
5	2	9.4	f	periorbital heamatoma	Von-Willbrand disease
6	4	20	m	epistaxis	idiopatic thrombocytopenia
7	8	26	f	gum bleeding	Von-Willbrand disease
8	5	25	f	heamaturia	idiopateic thrombocytopenia Purpura (I.T.P)
9	7	22	m	bleeding after tooth extraction	Heamophelia
10	6	28	f	large brusies in Rt. Leg after trauma	Von-Willbrand disease
11	3	16	f	epistaxis	Von-Willbrand disease
12	7	21	m	heamarthrouis Rt. Knee	Heamophelia
13	8	22	m	epistaxis after blunt trauma	Heamophelia
14	5	15	m	heamatamesis	Liver cirrhaus & oesoph. Varians
15	2	12	f	heamaturia	I.T.P.
16	10	30	m	gum bleeding	heamophelia

Table 2: Neonates with bleeding

No.	Age (y)	Weight (kg)	gender	Presentation	Diagnosis
1	12	3	m	Heamatamis + Malena	Sepsis + DIC
2	15	2	f	Heamatamis + Epistaxis	Sepsis + DIC
3	17	3.5	f	Heamatamis + Epistaxis	Sepsis + DIC
4	10	3.3	m	Malena	Sepsis + DIC
5	13	3	f	Heamatamis + Malena	Sepsis + DIC
6	23	3	m	Heamatamis + Malena	Sepsis + DIC
7	19	3.9	f	Heamatamis + Malena	Sepsis + DIC
8	11	3.2	f	Heamatamis + Malena	Sepsis + DIC
9	3	2.3	f	Umblical bleeding+Malena	Vit. K deficiency & NNJ
10	30	4.1	m	Heamatamis + Malena	Sepsis + DIC
11	21	3.9	f	Heamatamis + Malena	Sepsis + DIC
12	20	3	m	Epistaxis + Heamatamis	Sepsis + DIC
13	2	3	m	Heamatamis + Malena	Vit. K deficiency
14	3	2	f	Heamatamis + Malena	Vit. K deficiency
15	18	1.6	m	Heamatamis + Malena	D.I.C
16	20	2.2	m	Heamatamis + Malena	Sepsis +
17	3	3	f	Umblical bleeding	Vit. K deficiency
18	16	2.1	m	Heamatamis + Malena	sepsis & G. E.
19	30	3.6	f	Epistaxis + Heamatamis	sepsis + broncho-pneumonia

Table 3: RF Vlla treatment and outcome in control group

No.	Dose µg/kg	R Period	gender	Presentation
1	12	single dose	m	Heamatamis + Malena
2	15	single dose	f	Heamatamis + Epistaxis
3	17	single dose	f	Heamatamis + Epistaxis
4	10	single dose	m	Malena
5	13	every 8 hours for 3days	f	Heamatamis + Malena
6	23	single dose	m	Heamatamis + Malena
7	19	single dose	f	Heamatamis + Malena
8	11	single dose	f	Heamatamis + Malena
9	3	single dose	f	Umblical bleeding+Malena
10	30	every 8 hours for 3days	m	Heamatamis + Malena
11	21	single dose	f	Heamatamis + Malena
12	20	every 8 hours for 3days	m	Epistaxis + Heamatamis
13	2	single dose	m	Heamatamis + Malena
14	3	single dose	f	Heamatamis + Malena

15	18	single dose	m	Heamatamis + Malena
16	20	single dose	m	Heamatamis + Malena

Table 4: RFVlla treatment and Neoneates and Outcome

No.	RFVlla dosage	Treat-ment Period	Additional treatment	Outcome	Diagnosis
1	90µg/kg	every 8 hrs. for 3days	non	Bleeding stopped	Discharged well
2	90µg/kg	every 8 hrs. for 2days	non	Bleeding stopped	Discharged well
3	90µg/kg	every 8 hrs. for 1days	non	Bleeding stopped	Discharged well
4	90µg/kg	single dose	non	Bleeding stopped	Discharged well
5	90µg/kg	4 doses 8 hourly	non	Bleeding stopped	Discharged well
6	90µg/kg	single dose	non		Discharged well
7	90µg/kg				Discharged well
8	90µg/kg	single dose	non		Discharged well
9	90µg/kg	every 8 hrs. for 2days	non		Patient got TSP over 20mg/dl & Rh incompatibil-ity. No need for exchange trans-fusion & and TSB later on 12 mg/dl
10	90µg/kg	2 doses	1 packed RBC		Discharged well
11	90µg/kg	every 8 hrs. for 4days	1pint plasma & Vit. K ampule 5mg i.v.	Died of low plettlet (less than 150k)	non
12	90µg/kg	every 8 hrs. for 4days	non	discharged well	
13	90µg/kg	single dose	non	Died	non
14	90µg/kg	single dose	non	discharged well	non
15	90µg/kg	every 8 hrs. for 5days	1 packed RBC cell	discharged well	non
16	90µg/kg	single dose	non	discharged well	
17	90µg/kg	single dose	non	discharged well	non
18	90µg/kg	single dose	non	discharged well	non
19	90µg/kg	single dose	non	discharged well	non

5. Discussion

In our study, it has been found that RFVIIa dose was effective even as low as (40 µg/kg) and the efficiency in stopping bleeding are comparable with (90 µg/kg) doses. In Congenital Factor VII deficiency, doses as low as (15-30 µg/kg) and even (10µg/kg/dose), were found to be effective [4].

RF Vila is a safe drug used to stop bleeding in multiple he-matological disorders and it has shown to improve the lab parameters (P.T., P.T.T., and PCV%), decrease blood loss, decrease blood products used in children above 1 year of age [8].

The on-label use was approved by (Food and Drug Administration - PDA) in U.S.A as in hemophilia with inhibitors, deficiency in factor VII, pre-and post-operatively, and Glenzmann's Thrombosthenia [9, 10].

There is a wide use of the off-label RF Vila in children and neonates more than the on-label, because the congenital de-ficiency of factor VII and hemophilia are rare disorders compared to the other neonatal bleedings such as: asphyxia, D.I.C, sepsis and others. Congenital hematological disorders are rare and difficult to diagnose in neonates [11, 12].

The off-label use of RF Vila in neonates with D.I.C, and liver disease was shown to decrease bleeding but increase the risk of thrombosis [13], the risk of thromboembolism in children is higher than adults because children have high clearance rate of RFVIIa than adults. The risk of thromboembolism was found to be 5.4% in neonates and children while in adults it is lower than that [7].

In our study there the risk of thromboembolism is not dose dependent, nor the number of doses [14]. It has been found to occur at a dose as low as 35ug/Kg [15].

The doses of RFVIIa that was used in our study were (90 µg/Kg) in all patients, except in one occasion, because of the shortage in the drug supply to our hospital.

In congential factor VII deficency, the dose is 15-30µg/Kg/dose and could be 10µg/Kg/dose were found to be effective [4].

The early use of RF Vila in patients with sepsis and bleeding is the most important point in our study. It must be used as early as possible when the platelet count is normal or near to normal and not below 150x109 nor when the patient is presented late and with severe interactable bleeding [16].

When there is a sever infection, as in our study group patient who died, there is a high consmption of coaglation factors which leads to bleeding and in late stages there will be micro-vascular thrombus formation with multi-organ failure and D.I.C. therefore the drug is not effective at this stage [17, 3]

6. Conclusion and Recommendations

RFVIIa is a promising drug and lifesaving due to its effi-cacy and safety. There was a success rate of 91.4% in our study with no obvious side-effects and the mortality rate was 8.5%.

In the duration of our study it has been found that patients who had normal to high levels of plateltes had a better response and survival rate than patients with low

platelet count. Therefore, RF Vila must be given early stages of bleeding. It has also been found that when using RF Vila to stop bleeding in some patients with neonatal jaundice, there was a rapid decrease in TSB, reducing the time of the used phototherapy and decreases the need for exchange transfusion even in the presence of Rh-incompatibility. Therefore, the effect of RF Vila on hemolytic anemia and jaundice needs to be studied further more in the future.

References

[1] Ulla Hender, "Recombinant Factor Vila: 30 years of research and innovation", Blood reviews, vol.29, issue 1, Jun., 2015, pp. 54-58.
[2] HeseCosar, HalilIsikSalih, CagriCakir, NeseYar, Bulent Goksen, HakanTokbay, Hasan Kertmen, NihalErdogan, IkbalDurak "Recombinant factor VII treatment in very-low birth weight premature infants with acute pulmonary hemorrhage (A single center retrospective study)", vol. 19, issue 1, Feb., 2017, pp.53-58.
[3] Marcel Levi, and Tom Van DerPoll, "coagulation and sepsis", vol. 149, Jan., 2017, pp.38-44.
[4] Novo-Nordisk, "Novo-Seven Coagulation Factor Vila (Recombinant)"
[5] ReuteGurion, Anita Siu. Aaron R. Weiss, Margaret Masterson,"Use of Recombinant Factor VII in pediatric patient with initial presentation of refractory acute immune thrombocytopenic purpura and severe bleeding", The journal of pediatric pharmacology and therapeutics, vol. 17, issue 3, Jul.-Sep., 2012, pp.274-280.
[6] Ellis J. Neufeld,ClandeNegrier, Per Arkhqammar, Soraya Benchikh el Fegoun, Mette DuelundSimonsen, Andres Rosholom, Stephanie Seremetis "Safety-update on the use of RF Vila in approved indications", Blood reviews, vol.29, issue 1, Jun., 2015, pp.534-541.
[7] CattivelliK, Distefano C,Bonetti L,Testa S,Siboni S.M., Plebani A., Poggiani C."Recurrent bleedings in newborn: A factor VII deficiency case report", Transfusion medicine and hematology, vol. 45, 2018, pp.104-106.
[8] Blatny, Jan; Mathew, Prasad; Monagle, Paul; Ovesna, Petra; Fiamoli, Veronika, "Safety and efficacy of RF Vila in non-hemophilic children with severe or life threatening bleeding: A report from the seven bleep registry", blood coagulation and Fibrinolysis, vol. 25, issue 4, Jun., 2014, pp.326-332.
[9] K.amano, I. Seita, S. Higasa, A. Sawada, M. Kuwahara, M. Shima "treatment of acute bleeding in acquired hemophilia A with Recombinant Factor Vila", Wiley library/hemophilia, vol.23, issue 1, Jan. 2017, pp. 50-58.
[10] Margret V. Ragni, "novel alternate hemostatic agents for patients with inhibitors: beyond by-pass therapy", American society of hematology, issue: 2017, Dec., 2017, pp.605-609.
[11] Joh Putez, "Overview of the use of RF Vila in children", pediatric health medicine and therapeutics, vol. 5, 2014, pp.141-148.
[12] Chi N. Dang, Lakshmi I Katakam, P. Brian Smith, C Michael Gotten, Ronald N Goldberg, Nicole Chandler, Courtney D Thornburg, and Margarita Bidegain, "RF Vila treatment for refractory hemorrhage in infants", Journal of perinatology, vol. 31, issue 3,Mar., 2011, pp.l88-192.
[13] Jennifer Davila, "coagulation disorders in the newborn", Neoreviews/American academy of pediatrics, vol. 19, issue 1, Jan., 2018, pp.11-21.
[14] ZoekK.McQuilten, Barnes Chris, Zatta Amanda, Phillips Louise E."off-label use of RF Vila in pediatric patients", Neoreview Plus, vol. 129, issue 6, 2012, pp. 1533-1540.
[15] Stacy E. Croteau, Charles Nakar, Ellis J. Neufeld, Amy Shapiro, David L. Cooper, "Safety and efficacy of RF Vila by pediatric cohort: Reassessment of compassionate use and trial data supporting U.S label", pediatric blood and cancer/New York Academy of Sciences, Wiley Library, vol. 63, issue 10, Oct., 2016, pp. 1822-1828.
[16] A.Venugopal, "disseminated intravascular coagulation", Indian Journal of anesthesia, vol.85, issue 5, Sep-Oct.2014, pp. 603-608.
[17] Jeff Simmones, and Jan-Francois Pittet," the coagulopathy of acute sepsis", current opinion in anesthesiology, vol. 28, issue 2, Apr., 2015, pp. 227-236.