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Iraqi Experience of Factor VII use in Children

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ABSTRACT

Bleeding disorders in pediatrics is an important issue and can be life-threatening if not diagnosed and treated appropriately. We aimed to evaluate Iraqi pediatric practice (as an example of resource-limited settings) about the use of Recombinant Activated Factor VII (RFVIIa) in bleeding disorders, with emphasis on its effectiveness and safety, in comparison with adjuvant therapy. Budget restrictions may affect the availability of even lifesaving drugs such as (RFVIIa). Therefore, we tried to investigate the local experience of pediatric bleeding, with the evaluation of the potential ability of adjuvant therapy of blood products and vitamin K to substitute RFVIIa in case of non-availability. During a complete one year's period, 35 patients were recruited prospectively and divided into two categories; study group (on RFVIIa, with or without adjuvant therapy) and control group (only on adjuvant therapy of blood products, and vitamin K), involving 19, and 16 patients, respectively. The mortality rate in the study group was significantly less than the control group; (36.84%) versus (56.25%). Larger drops in prothrombin time (PT) (42%), and partial thromboplastin time (PTT) (47%), with less multi-organ dysfunction (29%) were noticed with the use of RFVIIa. Septicemia-associated disseminated intravascular coagulation was the most frequent indication of both groups; (31.58%) versus (37.50%), with a significant positive outcome in the study group. Total serum bilirubin levels were found to be lower in all neonates with jaundice within the study group. One patient had venous thrombosis following the RFVIIa administration. In conclusion, RFVIIa has the potential to stop pediatric bleeding episodes significantly better than adjuvant therapy alone, with significantly less mortality. Safety was ensured in all survived cases except one who had thromboembolism. Neonatal jaundice was improved by the use of RFVIIa.

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INTRODUCTION

In bleeding disorders; Efforts to stop bleeding and secure hemostasis are considered as a priority with the use of minimum need of therapy (Poon, 2019).

One of the most promising therapies is the Recombinant Activated Factor Seven (RFVIIa) (Cosar *et al.*, 2017).

This drug was first used in the early seventies of the last century for the treatment of blood disorders such as hemophilia with low thromboembolic side effects. However, there is an increasing trend of off-label indications, like in high-risk bleeding as prophylaxis before surgical procedures (Al-Momen

et al., 018b; Hedner, 2015; Levi and Poll, 2017).

The safety of RFVIIa is due to its recombinant nature and site of its action on the activated platelets located at the injury position only (Neufeld *et al.*, 2015).

The goal of this study to put the Iraqi pediatric experience of RFVIIa usage into a glance, as it has budget limitations and restricted resources, and also to investigate the safety and effectiveness of RFVIIa and adjuvant therapy in the treatment of various hemorrhagic disorders in pediatrics.

MATERIALS AND METHODS

This prospective study was performed in Bleeding Tendency Centers at Kut and Karbala in Iraq, started from the first of July, 2017 till the end of June, 2018. Although these centers provided free tertiary services and received patients from all over the governorate borders, full medical requirements (including drug availability) were not always perfect because of fund limitations.

We involved 35 patients at different ages (from the age of one day – 12 years old). All patients visiting the above centers complaining from bleeding disorders were divided into two categories according to the availability of RFVIIa at time of presentation; "study group" with 19 patients whom got RFVIIa with or without adjuvant therapy (blood, blood products, and vitamin K), and "control group" which consisted of 16 patients whom treated by adjuvant therapy only without the use of RFVIIa.

The approval of the scientific and ethical committee of Al-Kindy College of Medicine, University of Baghdad, was taken to perform this study, and work was done according to the principles outlined in the Declaration of Helsinki.

Written informed consent was obtained from parents or guardians of all involved patients.

The tests used were; Complete blood count (CBC), blood film, prothrombin time (PT), partial thrombin time (PTT), total serum bilirubin (TSB), blood culture with sensitivity, and fibrinogen level when available. These tests were done within 4-5 hours before and after the first (or the only) dose of RFVIIa. If multiple doses had to be given $\geq$ 24 hours apart, the second dose was considered as another separated one. Adjuvant blood products (or adjuvant therapy) were recognized as a progressive total amount of packed red blood cells, fresh frozen plasma (FFP), platelets, vitamin K, and cryoprecipitate administered alone, or up to 24 hours pre- and post- RFVIIa. Scores of pediatric risk of mortality (PRISM) were calculated (Pollack *et al.*, 1988). Depending on consensus criteria, we were able to identify any organ dysfunction at the time of treatment (Weiss *et al.*, 2014).

RFVIIa was used in a dose of 90 μg\ kg in all the patients. Some of them were given a single dose and responded well with the cessation of bleeding; others needed multiple doses for a few days to respond. RFVIIa was given by intravenous transfusion slowly and under close medical supervision over 30 minutes.

A follow -up period of two weeks after RFVIIa was suggested to identify related thromboembolic side effects by means of medical history and examination performed by the attending pediatrician, radiographic, and as-needed laboratory investigations. Patients who failed to be followed up were excluded.

Statistical work was done using Statistical Package for the Social Science, IBM SPSS version 20.0 (IBM SPSS Statistics, Armonk, NY). Median measures represented continuous data variables with interquartile range (IQR). Fisher's test paired t-test, and the Mann- Whitney test was used for categorical variables, paired continuous variables, and independent continuous variables, respectively. Statistical significance was touched when $p \leq 0.001$.

RESULTS AND DISCUSSION

In the study group, 7 out of 19 patients (36.84%) died, while the mortality in the control group was 9 out of 16 (56.25%). Accordingly, the survival rate, or we may consider it as the success rate of treatment when RFVIIa was used in the study group, was (63.16%). It was only (43.75%) when RFVIIa not used in the control group. These are statistically significant values ($p \leq 0.001$).

Moreover, 16 patients (84.21%) of the study group did not need adjuvant therapy in addition to RFVIIa to take control over hemorrhage. In survivors of this group, 10 patients out of 12 were on RFVIIa alone, which represented (83.33%).

Both groups had comparable parameters of age, gender, and the start levels of PT and PTT before treatment. Also, platelet counts were comparable and around normal laboratory limits (or slightly below), but these counts were low (< 100 000/ mm^3) on presentation, in all patients who died in both groups.

The study group had statistically significant less frequent doses of treatment therapy, less mortality score, and less multi-organ failure (such as liver, renal and circulatory failure), with a significant drop in PT, and PTT after treatment (RFVIIa with or without adjuvant therapy). All of the above is evident in

Table 1: General characteristics of patients involved

Variable	Study group, (no = 19)	Control group (no = 16)	P-value
Sex, male: female	10: 9	8: 8	0.538
Age, median (IQR), months	12 (0.8- 152)	14 (0.9- 158.5)	0.103
Multiple courses of treatment (RFVIIa, or adjuvant therapy), %	56%	91%	$\leq$ 0.001
PT before RFVIIa, median (IQR), seconds	21.3 (15.4- 24.6)	24.1 (17.2- 28.3)	0.034
PTT before RFVIIa, median (IQR), seconds	45.6 (35.6- 57.8)	44.2 (37.4- 55.1)	0.119
Decrease of PT after RFVIIa and/ or adjuvant therapy %, median (IQR)	42% (19- 51)	11% (5- 32)	$\leq$ 0.001
Decrease of PTT after RFVIIa and/ or adjuvant therapy %, median (IQR)	47% (25- 54)	12% (7- 48)	$\leq$ 0.001
Platelet count on RFVIIa, and/ or adjuvant therapy, median (IQR), 109/L	117 (46- 198)	122 (53- 209)	0.208
PRISM score, median (IQR)	12.6 (10- 25)	27.4 (13- 32)	$\leq$ 0.001
Multiple organ failure ($\geq$ 3), %	29%	68%	$\leq$ 0.001

Table 2: Causes of bleeding related to their outcomes

Cause of bleeding or indication of RFVIIa and/ or adjuvant therapy, no (%)	Study group (no, 19)			The control group (no, 16)			P-value
	Total	Alive patients, no (%)	Dead cases, no (%)	Total no (%)	Alive patients, no (%)	Dead cases, no (%)	
DIC(disseminated intravascular coagulation) and/ or sepsis	6 (31.58%)	3 (50.00%)	3 (50.00%)	6 (37.50%)	1 (16.67%)	5 (83.33%)	$\leq$ 0.001
Gum bleeding and /or epistaxis	5 (26.32%)	4 (80.00%)	1 (20.00%)	4 (25.00%)	3 (75.00%)	1 (25.00%)	0.287
GIT bleeding (hematemesis and/ or malena)	4 (21.05%)	2 (50.00%)	2 (50.00%)	3 (18.75%)	1 (33.33%)	2 (66.67%)	0.350
Hemarthrosis	3 (15.79%)	2 (66.67%)	1 (33.33%)	2 (12.50%)	1 (50.00%)	1 (50.00%)	0.013
*Prophylaxis of a procedure or	1 (5.26%)	1 (100.00%)	0 (0.00%)	1 (6.25%)	1 (100.00%)	0 (0.00%)	1.000
**CNS bleeding							

*The procedure was renal biopsy, in study group. No bleeding bouts had occurred afterwards.
**CNS(central nervous system) bleeding due to trauma (macrosomic baby), in control group.

Table 1.

The most common cause of death in both groups is DIC (disseminated intravascular coagulation) with or without sepsis; its related mortality rate was higher and statistically significant in the control group.Gum bleeding and /or epistaxis, GIT (gastrointestinal tract) hemorrhage, hemarthrosis, and procedure prophylaxis came after in frequency, in a respective way. Mortality rates related to these causes were also higher in the control group, but they did not touch significance levels, as illustrated in Table 2.

Only one patient (5 years old male) from the study group had thromboembolism. He was diagnosed with hemophilia complicated by severe GIT bleeding (hematemesis and melena). He was given 3 successive doses of RFVIIa every 4 hours on admission, with one dose of FFP, then the bleeding stopped. After 36 hours, the patient had sudden deterioration in the conscious level. A computed tomography (CT) scan of his brain showed no recent hemorrhage, just cerebral edema. The child was then referred for a neurosurgical consultation and they replied with venous sinus thrombosis. They did every effort to save him, but he died 3 days later.

The accidentally discovered surprising fast decrease in total serum bilirubin of involved neonates (in the study group) having neonatal jaundice within their hospital stay, inspired us to plot Figure 1, where all neonates took the same management, like phototherapy and exchange transfusion when needed. Study group patients who received RFVIIa had the ability to lower their TSB levels more effectively than patients who did not receive RFVIIa, whatever the cause of bleeding was. Neonatal jaundice was hemolytic and caused by either physiological or pathological etiologies.

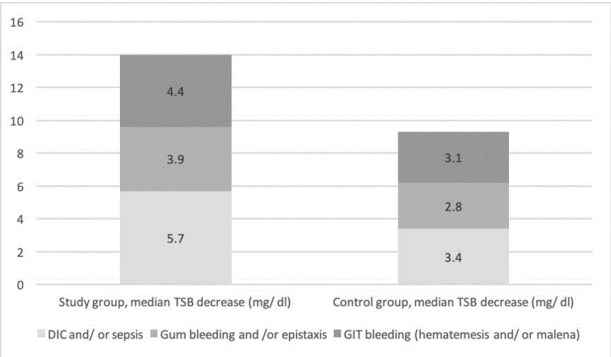

Figure 1: Drops of bilirubin in both involved groups

Large controlled trials that talked about safety, effectiveness and the whole experience of RFVIIa in pediatrics are rare, in contrary to adults. However, many case reports and some small original articles are available (Agarwal *et al.*, 2007; Brady *et al.*, 2006; Pettersson *et al.*, 2005; Reiter *et al.*, 2007; Morenski *et al.*, 2003).

We tried to summarize our prospective local Iraqi experience of the management of pediatric bleeding disorders as an example of third world countries, where RFVIIa is available sometimes and in other times not.

To prove the effectiveness of RFVIIa, we noticed a significant drop in PT, and PTT in treated patients, just like other reports which confirmed that these drops in laboratory values would reflect the effective anticoagulation action of RFVIIa (Levi *et al.*, 2005; Reiter *et al.*, 2007).

However, other reporters assumed that PT is an inaccurate tool for effectiveness (Vincent *et al.*, 2006).

The use of RFVIIa as a monotherapy without any added adjuvant medications to treat bleeding episodes in survivors was achieved in (83.33%) in our data, which may be another indicator of effectiveness, with the advantage of lowering the risk of blood products (adjuvant therapy) associated disorders, such as transfusion transmission of infections, acute lung injury, and hemolytic anemia (Agarwal *et al.*, 2007; Jasim *et al.*, 2018; Blajchman and Vamvakas, 2006; Fager *et al.*, 2018).

Platelet counts on presentation were low in all patients who died, whether they took RFVIIa or adjuvant therapy, which could be used as a prognostic indicator for these cases. Other papers put down that the higher the platelet count during bleeding episodes, the better the outcome (Fager *et al.*, 2018; Poon, 2019).

Sepsis- associated DIC was the most common cause of coagulopathy in our series, but growing worries were found about the use of RFVIIa, as platelets and monocytes express tissue factor with the resultant of increasing thrombosis risk and more deterioration in DIC (Levi and Scully, 2018). In spite of the statistically significant effectiveness of RFVIIa that we found in sepsis/ DIC patients, still half of them died, unlike previous reports (Chuansumrit *et al.*, 2005; Tobias *et al.*, 2003). These patients who passed away were critically ill and presented late to our clinics, which may have an impact on the total results, in line with other articles that stated that RFVIIa usage in life-threatening conditions would not lead to a better survival rate (Biss and Hanley, 2006; Bowles *et al.*, 2006; Clark *et al.*, 2004).

This is particularly an important issue; the clinician should have the skills to expect possible outcomes

when RFVIIa is to be decided. It is a costly branded drug that is not always obtainable, especially in our part of the world, with restricted financial plans set for the medical field and the wide availability of different substandard drugs in the market (Daher *et al.*, 2019; Mattar *et al.*, 2018; Jasim *et al.*, 2019).

Administration of RFVIIa leads to better bleeding control in different indications, like gum, nose, and GIT bleedings, and hemarthrosis. RFVIIa remains the backbone of any management guidelines to control bleeding events (Cooper and Ritchey, 2017; Park and Kim, 2015).

Herein this study, RFVIIa was as effective as adjuvant therapy in prophylaxis prevention of bleeding due to procedural works, but others opposed this (Fager *et al.*, 2018).

We cannot depend on our data as it was very limited, only one patient within the study group.

Intracranial bleeding due to head trauma resulted from neonatal macrosomia was effectively treated with adjuvant therapy only, as FFP is considered beneficial here in spite of some delay in response and frequent doses (Al-Momen *et al.*, 018a; Morenski *et al.*, 2003).

Arterial and venous thrombosis related to the use of RFVIIa in patients without hemophilia diagnosis are arising concerns (Downey *et al.*, 2017; O'connell, 2006).

Pediatric ages have less risk of thrombosis than adults because children have a higher clearance rate of RFVIIa, and they lack disseminated atherosclerosis process (Brady *et al.*, 2006).

Only one patient from our sample had a proved thromboembolic event (sinus venous thrombosis).

Neonatal jaundice was better improved in patients receiving RFVIIa than adjuvant therapy, the drop of TSB levels was higher in a shorter period, although all neonates were treated independently with a traditional regimen of phototherapy, and exchange transfusion as needed according to the hospital guidelines Al-Momen *et al.* . Up to our knowledge, no one previous report had mentioned any relationship between RFVIIa and TSB, hemolysis, and neonatal jaundice. Despite the fact that this finding was discovered accidentally in our small sample of neonates, it may be due to correction of liver clotting factors that would lead to some sort of liver enzymes refreshment, which might lead to better liver performance to deal with this excess circulating bilirubin, even if this bilirubin is indirect (due to hemolysis). Or there may be an unknown mechanism to lower down the progressiveness of the neonatal hemolytic process. In addition, these results may be odd findings linked to certain circumstances related to our neonates, and living environment; climate temperature, humidity, and altitude are examples. We strongly encourage other researchers from different parts of the world to focus on this issue in more oriented trials with a larger number of patients.

This data is limited by its small-sized sample. Not all causes of bleeding that indicated treatment with RFVIIa were presented to our centers within the study period. Also, groups of patients were divided on the basis of out of control absence of RFVIIa because of restricted resources.

On the other side, being more optimistic, and based on our follow up, this data is the largest one done in Iraq, and reflected the real practice that took place in this country, which in turn looks like what is found in most of the third world countries. However, we were able to define specific observations and new findings about the Recombinant Activated Factor VII regarding safety and effectiveness.

CONCLUSIONS

Recombinant Activated Factor VII administration is significantly associated with less mortality rates, PT, PTT, and less frequent courses of treatment, and multi-organ failure, than adjuvant therapy (blood products, and/ or vitamin K). RFVIIa is doing well in bleeding events resulted from DIC and/ or sepsis, gum bleeding and /or epistaxis, GIT bleeding (hematemesis and/ or melena), and hemarthrosis. Adjuvant therapy alone shows less ability to treat the indications, as mentioned above, with higher death rates. Treatment with RFVIIa in neonates is associated with less TSB readings and less severity of hemolytic jaundice. As a final word, RFVIIa is more effective than adjuvant therapy and is considered as a safer way to be used in bleeding disorders during pediatric practice.

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