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Full Length Research Paper

The Impact of Recombinant FVIIa Infusion on Transfusion Requirements in Bleeding Patients

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Recombinant factor VIIa (rFVIIa) is approved for treatment of bleeding in congenital hemophilia patients with inhibitors, but is also used for myriad off-label indications. Currently, rFVIIa is frequently used to control bleeding in critically ill and surgical patients despite the paucity of evidence. We report here on transfusion requirements before and after rVIIa infusion in patients treated for off label indications. All off-label episodes of treatment with rFVIIa at King Abdulaziz University Hospital over 12 months were included. Data were extracted using a standardized case report form. Relevant laboratory and clinical variables were collected. Transfusion requirements pre and post treatment with rFVIIa , were compared for various clinical indications. Seventy patients were included with a mean age of 46.1 (± 18.6) years. The four most common off-label indications for rFVIIa treatment were for bleeding associated with cardiac surgery (33.3%), management of intracerebral hemorrhage (ICH) (18.8%), post partum hemorrhage (PPH) (11.6%) and bleeding varesis (13%). Comparison of the median number of blood product units required pre- and post- rFVIIa treatment revealed a significant reduction in transfusion requirements following rFVIIa treatment. Our results indicate that off-label use of rFVIIa treatment is associated with a significant reduction in transfusion requirements in patients with surgical and obstetric hemorrhage.

Keywords: Bleeding, Recombinant factor VIIa, transfusion requirements

INTRODUCTION

Recombinant FVIIa (rFVIIa) (rFVIIa; NovoSeven, Novo Nordisk A/S, Bagsværd, Denmark) is produced commercially by transfecting the human FVII gene into cultured hamster cells. The action of high-dose rFVIIa is dependent upon both tissue factor and platelets (Hedner and Lee, 2011). In non-hemophilic patients, platelet-bound rFVIIa increases both FIX and FX activation and ultimately thrombin generation (Hedner and Lee, 2011).

Native factor VIIa (FVIIa) was first shown in 1983 to be effective for treatment of bleeding hemophilia patients with inhibitors (Hedner and Lee, 2011). The Food and Drug Administration (FDA) approved recombinant FVIIa in the United States in 1999 for that indication. The label was expanded in 2004 to include use in patients with Glanzmann's thrombasthenia with past or present history of platelet refractoriness to platelet transfusions by the European Medicines Agency and in 2005 to include patients with congenital FVII deficiency. In 2006, the FDA approvedrVIIa for use in patients with acquired hemophilia.

Uncontrolled bleeding continues to be a major cause of mortality in trauma(Kauvar et al., 2006), cardiac surgery(Woodman and Harker, 1990), postpartum hemorrhage (PPH) (Khan et al., 2006), and intracranial

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hemorrhage (ICH) (Johnston et al., 1998). rFVIIa is increasingly being used off-label for restoring hemostatic balance in these conditions. The risks of blood transfusion are numerous including transfusion reactions and alloimmunization; thus unnecessary transfusions should be avoided (Engelbrecht et al., 2013). A randomized controlled trial on rFVIIa in trauma patients reported significantly reduced packed red blood cell (PRBC) transfusion (Boffard et al., 2005).

In this study, we report on the effect of rFVIIa infusion on transfusion requirements in a heterogeneous group of patients with clinically relevant bleeding.

MATERIALS AND METHODS

Patient data were collected by review of medical records after obtaining approval of the hospital ethics committee. We excluded four patients (two pediatric patients as well as two adult patients) who received rFVIIa for FDA-approved indications. Recombinant FVIIa was administered at the discretion of the treating physician, in the absence of local guidelines. All patients received rFVIIa for major or life-threatening hemorrhage when other measures failed including; surgical interventions, blood component therapy, and other hemostatic agents including; antifibrinolytic agents, 1-deamino-8-D-arginine vasopressin [DDAVP]. Data collected were demographics, baseline coagulation screen and number of units of blood component transfused during the 24 hours preceding and the 24 hours immediately following rFVIIa administration. Laboratory test results closest to the timing of rFVIIa administration were collected.

Statistical analysis

All analyses were conducted using IBM SPSS version 22. A P-value of <0.05 was considered statistically significant. Frequency statistics were used to show descriptive statistics for the mean, range, and variations of the variables; including complete blood counts, coagulation profile, gamma glutamyl transferase, creatinine kinase, troponin, and serum creatinine. The paired t-test and Wilcoxon test were used to compare means with normal and non-normal distribution, respectively. To establish the demographic relationship to these variables, the chi-square test was used for the categorical variables. To relate differences in variables to these domains, the t-test and one-way analysis of variance (ANOVA) were used to compare the mean from two groups and >2 groups, respectively. Normality was assumed using the Levene test for homogeneity of variance. If there was unequal variance, the Welch t-test was used as an alternative to the standard t-test, and a post-hoc test least significant difference was used as an alternative to one-way ANOVA. Where $P < 0.05$ was a criterion for rejecting the null hypothesis, power analysis was used to measure the strength of sample differences.

Continuous variables within groups were analyzed with paired t-test, and independent t-test between groups. Categorical variables were compared via chi2 or Fishers Exact test and significance was denoted by a $p <$ or $= 0.05$.

RESULTS

Patients

Seventy consecutive patients who presented over a period of 12 months were included thirty-seven female patients (52.9%) and 33 male patients (47.1%). (Table 1) The mean age was 46.11 (± 18.6) years.

Indications for FVIIa Use

Off-label indications for FVIIa use are shown in Table 1. The most common off-label uses of rFVIIa were bleeding following cardiac surgery (33%), ICH (18.8%), and PPH (11.6%). Other indications included gastrointestinal tract (GIT) bleeding due to uremia and liver disease (13%), and bleeding in cancer patients (7.2%).

Laboratory values

Laboratory test results were collected prior to rFVIIa administration and are shown in Table 2.

Transfusion requirements

The paired-sample t-test revealed that administration of rFVIIa was followed by a significant reduction in the requirement for PRBC ($P < 0.001$), fresh frozen plasma (FFP) ($P < 0.001$), and platelets ($P < 0.001$) but not for cryoprecipitate ($P = 0.262$) (Figure 1) (Table 3).The mean number of packed PRBC units, FFP units, platelets units and cryoprecipitate units required, before and after rFVIIa administration, were 3 and 0.8 units ($p<0.001$), 4.8 and 1.9 units ($p<0.001$), 2.8 and 1.0 units mL ($p<0.001$), 1.6 and 1.0 units ($p=0.262$), respectively.

Transfusion requirements by indication

Transfusion requirements before and after rFVIIa infusion were compared by most common off-label indications. (Table 4) In cardiac surgery, transfusion requirement for all components was reduced except for cryoprecipitate requirement. In ICH, only FFP transfusion was significantly reduced following rFVIIa administration. In PPH, PRBC and FFP transfusion requirements were significantly reduced. Thus, FFP requirements were reduced in all major off-label indications following rFVIIa infusion.

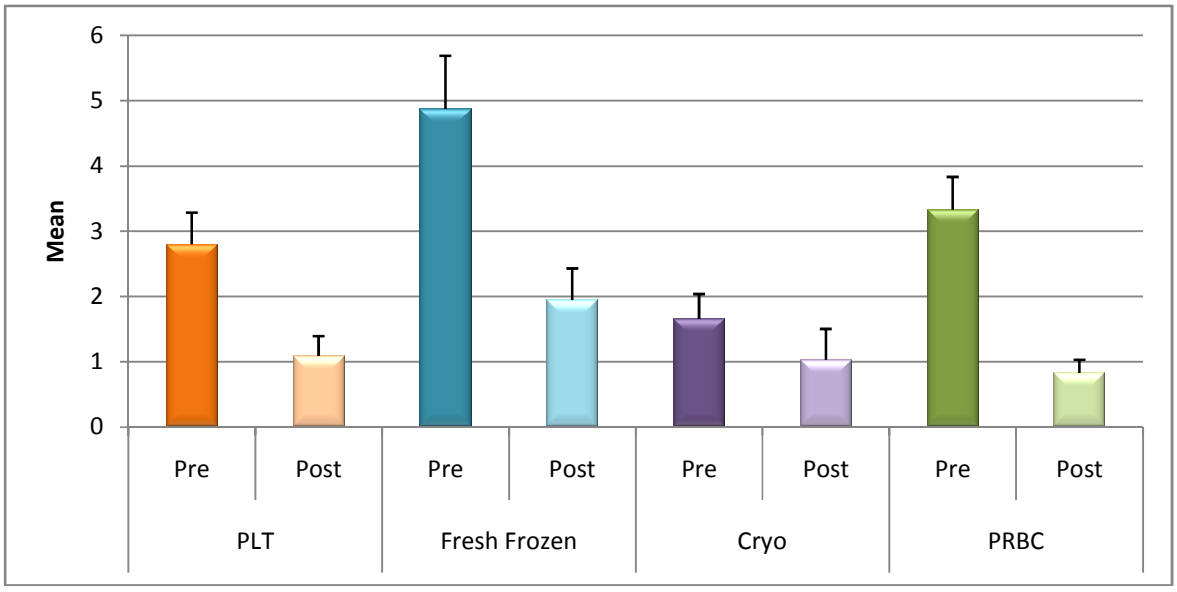

Figure 1. Blood product requirements before and after rFVIIa treatment

Blood products transfused 24 h before and after the administration of rFVIIa. Data presented are the mean of transfused blood components. PRBC, packed red blood cells; Fresh Frozen , fresh frozen plasma; Cryo, cryoprecipitate; Plts, platelet concentrate.

Table 1. Patients' demographics, survival, and indication for rFVIIa treatment.

		Minimum	Maximum	Mean	S.D
Age, year		**15**	**80**	**46.11**	**18.6**
		Count (n=70)		**Percent%**	
Sex	Male	33		47.1	
	Female	37		52.9	
Survival	Alive	40		58%	
Indication	Cardiac surgery	23		33.3	
	ICH	13		18.8	
	PPH	8		11.6	
	Bleeding varices	9		13.0	
	Malignancy and Others	8		11.5	

ICH, Intracranial hemorrhage; PPH, postpartum hemorrhage.

Table 2. Laboratory data at presentation.

	Minimum	Maximum	Mean	Std. Deviation	Mean +-SD
WBC count x10^9	.60	93.00	17.92	20.78	17+20
HB1 (g/l)	5.80	16.00	9.838	2.262	9.8+2.2
HB2 (g/l)	4.00	15.1	7.550	2.17	7.5+ 2.1
Platelets count (10^9 /l)	2.00	598.0	177.0	148.6	177+ 148
INR	1.00	7.20	1.613	1.274	1.6+1.2
APTT(seconds)	25.00	133.0	52.97	27.30	52 + 27
Fibrinogen (g/l)	11.00	981.0	346.2	212.7	346+ 212
D-dimer	11.70	2338.	711.7	550.9	711+ 550
Urea	1.50	64.00	11.08	12.45	11+12
Creatinine	1.84	1370.0	175.8	218.1	175+ 218

HB1, Hemoglobin at presentation; HB2, hemoglobin before rFVIIa treatment; INR, international normalized ratio; APPT, activated partial thromboplastin time; FIB, fibrinogen; ALT , Alanine transferase.

Table 3. Transfusion requirement in the 24 h before and after administration of rFVIIa treatment.

Variable	Mean ± SD		Mean difference	P-value
	Pre-rFVIIa	Post-rFVIIa		
PRBC	3.33 ± 4.2	0.83 ± 1.7	2.5	<0.001*
FFP	4.87 ± 6.8	1.94 ± 6.8	2.9	<0.001*
PLT	2.80 ± 4.0	1.09 ± 2.5	1.7	<0.001*
Cryo	1.66 ± 3.2	1.0 ± 3.9	0.6	0.262

PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, Platelet concentrate; Cryo, cryoprecipitate.
*Significant using paired sample t-test at 0.05 level.

Table 4. Blood component use before and after administration of rFVIIa by indication.

Indication	Variable	Mean ± SD		Mean difference (%)	P-value
		Pre-rFVIIa	Post-rFVIIa		
Cardiac surgery	PRBC	3.39 ± 3.7	1.26 ± 2.0	2.1	<0.001*
	FFP	5.96 ± 7.1	2.87 ± 4.9	3.1	0.019*
	PLT	4.35 ± 4.5	1.91 ± 2.7	2.4	0.013*
	Cryo	1.17 ± 2.2	1.74 ± 6.3	-0.6	0.703
ICH	PRBC	2.77 ± 4.9	0.31 ± 0.9	2.5	0.057
	FFP	2.38 ± 2.8	0.77 ± 1.9	1.6	0.030*
	PLT	1.17 ± 2.2	0.33 ± 1.2	0.8	0.147
	Cryo	0.69 ± 1.7	0.00 ± 0.0	0.7	0.168
PPH	PRBC	5.75 ± 5.6	0.88 ± 1.8	4.9	0.034*
	FFP	5.25 ± 5.7	2.13 ± 4.2	3.1	0.020*
	PLT	2.63 ± 2.6	0.75 ± 2.1	1.9	0.115
	Cryo	4.38 ± 3.5	2.00 ± 3.9	2.4	0.055

PLT, Platelet concentrate; FFP, fresh frozen plasma; Cryo, cryoprecipitate; PRBC, packed red blood cells; ICH, intracranial hemorrhage; PPH, postpartum hemorrhage.
*-significant using Paired-Sample t-test @ 0.05 level

DISCUSSION

Off-label use of medications is appealing when standard therapies prove to be ineffective. However, in the absence of randomized studies, the potential risk remains a major concern (Poon, 2001).

In this study, the most common off-label uses of rFVIIa were for cardiac surgery, ICH, and PPH, which is comparable to that of other registries(Logan et al., 2011)(Yank et al., 2011).

Cardiac surgery

Patients undergoing cardiovascular surgery facilitated by CPB may experience significant bleeding and roughly 80% require allogeneic RBC transfusions (Karkouti et al., 2010). Bleeding following cardiac surgery could be due to several contributing factors including crystalloid administration, heparin use, platelet consumption and platelet dysfunction caused by CPB(Schols et al., 2010).

The largest experience of rFVIIa usage in cardiac surgery comes from the Canadian, French and Australian and New Zealand registry which, showed a significant reduction in all blood products used (Karkouti et al., 2007) (Hacquard et al., 2011) (Dunkley et al., 2008). Cardiac surgery was consistently the largest indication reported to the ANZAR registry suggested that rFVIIa may be effective in reducing allogeneic transfusion (Dunkley et al., 2008).

A large phase II multicenter prospective randomized placebo-controlled trial showed a significant reduction in blood transfusion requirement (Gill et al., 2009).Similarly, our data show a significant reduction in transfusion requirements of FFP, platelet concentrate, and PRBC, but not cryoprecipitate, in cardiac surgery patients following rFVIIa administration.

Intracranial hemorrhage

Intracranial hemorrhage (ICH) can arise spontaneously or it can be induced by trauma or anticoagulation treatment and it is associated with 30-50% mortality rate. Recombinant FVIIa has been used in the management of spontaneous ICH (Mayer et al., 2005). In a multicenter

phase II study hematoma volume expansion was significantly decreased in the patients receiving rFVIIa, compared with placebo(Mayer et al., 2006).

Our findings indicate that patients received significantly less PRBCs and FFP transfusions in ICH, following rFVIIa administration.

Post Partum Hemorrhage

Severe Post Partum Hemorrhage (PPH) is encountered in less than 1% of deliveries however; it remains a significant cause of maternal death(Khan et al., 2006).

The Australian and New Zealand Haemostasis Registry includes the largest retrospective series and included data for 110 patients (Phillips et al., 2009). This study concluded that rFVIIa infusion results in a reduction in blood product use. The Italian Registry data supported these findings (Barillari et al., 2009). Despite limitations including the absence of a control group, heterogeneity of bleeding contexts, institutional variability and absence of a standardized protocol for rFVIIa administration, these studies mandate that participating hospitals provide complete patient capture, thus avoiding bias from selective case reporting.

Only 11% of the patients included in this study have received rFVIIa for PPH. Significantly less units of PRBC, FFP and cryoprecipitate transfusions were required following rVIIa utilization.

Study Limitations

Limitations of this study include the variable doses and timing of the administration of rFVIIa. Also, data on survival and treatment-associated adverse events were not available for all patients.

CONCLUSIONS

Clinical practice guidelines are devised to optimize timely and effective patient care while conserving resources. In the absence of high-quality evidence and considering the high cost of rFVIIa, there are concerns about its off-label use. This study supports a role for rFVIIa as a hemostatic agent that can significantly reduce transfusion requirements in cardiac surgery as well as intracranial and post partum hemorrhage following failure of first line measures. The role of rFVIIa in impeding hemorrhage and reducing transfusion requirements may help improve survival in these patient groups. Local and National guidelines are needed to optimize the utilization of rFVIIa for achieving hemostasis in clinically relevant bleeding in Saudi Arabia.

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