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Case Study

Recombinant Factor VIIa in Massive Bleeding at Hospital Universiti Sains Malaysia: A Retrospective Case Control Analysis

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ABSTRACT:

Introduction: Massive bleeding carries major clinical challenge as it needs to be managed in a limited time frame. Vigorous fluid resuscitation and massive transfusion has benefit to risk profile in terms of patient survival. This study aims to look at the indications and outcomes of non-haemophilia patients treated with and without rFVIIa during massive bleeding in Hospital Universiti Sains Malaysia (HUSM).

Methods: We conducted a retrospective case control analysis in Hospital Universiti Sains Malaysia KubangKerian, Kelantan from the year 2013 to 2016. 140 patients who fulfilled the inclusion and exclusion criteria were selected as the case and control group and were analysed. They were matched according to the causes of the massive bleeding.

Result: There were about 30 (42.9%) medical patients and 40 (57.1%) surgical patients who received rFVIIa. SOFA score of case group showed a higher mean score then the control group ($p = 0.038$) and was associated with overall survival of the case group ($p<0.001$). Further analysis noted that the surgical patients in the case group have better survival with lower SOFA Score ($p=0.001$). There was significant reduction in all the blood and blood product after initial dose of rFVIIa. No significant differences in thromboembolic event noted.

Conclusion: This study indicates the benefits of intervention with rFVIIa for management of massive bleeding in surgical patients with lower SOFA Score. A reduced in the amount of transfusion requirement observed with rFVIIa usage hence reducing the possible adverse effect of massive transfusion. There was no significant difference in thromboembolic complication between the groups hence safety profile of rFVIIa were proven.

Key words: *Massive bleeding, recombinant factor VIIa, SOFA Score, thromboembolic event*

How to Cite

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INTRODUCTION:

Massive bleeding is a medical emergency requiring immediate action and treatment. Prompt effective homeostasis and damage control resuscitation is of utmost importance because the mortality rate increases with increasing blood loss in both emergency and elective cases (Irita, 2011). According to Texeira et al, delay in hemorrhage control was a major cause of preventable or potentially preventable deaths in hospital (Teixeira *et al.*, 2007). Effective preparation and communication between transfusion and other laboratory services and clinical teams are essential regardless of massive bleeding aetiology (trauma, obstetrical, surgical) (Pham and Shaz, 2013).

Massive bleeding can be defined as blood loss exceeding circulating blood volume within 24 hour period, blood loss of 50% of circulating blood volume within a 3 hour period, blood loss exceeding 150ml/min or a blood loss that necessitates plasma and platelet transfusion (Irita, 2011). In addition massive transfusion is defined as transfusion of more than 10 units of packed red cells (RBC) within 24 hours or a corresponding blood loss of more than 1 to 1.5 fold of the body's entire volume (Meißner and Schlenke, 2012). Other definitions are transfusion of more than 4 packed RBC in one hour with anticipation of continued need for blood product support and replacement of more than 50% of the total blood volume by blood products within 3 hour (Pham and Shaz, 2013).

The traditional concepts of resuscitation in acutely bleeding trauma patients consist of aggressive fluid administration aiming at restoring intravascular blood volume. This approach, however, may contribute to further blood loss by increasing hydrostatic pressure on the clots, hypothermia, and dilutional coagulopathy (Chatrath *et al.*, 2015). Besides that, multiple complications such as circulatory overload may occur during an overzealous fluid resuscitation. This is not uncommon, especially during an intractable bleeding episode.

Recombinant activated factor VII (rFVIIa; Novo Nordisk, Copenhagen, Denmark) is a synthetic activated form of factor VII. It was originally developed for treatment of bleeding among hemophilia patients with antibodies (or inhibitors) against factors VIII or IX. Also known as a "bypassing agent", it acts by inducing thrombin generation and allow coagulation to take place without the need for (thus "bypassing") factors VIII and IX (Giansily-Blaizot and Schved, 2017).

Studies have shown that more than 95 % of rFVIIa usage was for off-label use among intractable bleeding patients. Even though the off-label use is still not proven to be associated with mortality benefit, there are literature showing an improved outcome (Karkouti *et al.*, 2005). The main concern on rFVIIa has been on safety issue of the increased risk of thrombotic complication (O'Connell *et al.*, 2006). It is still unclear which group of patients are the appropriate candidates for recombinant factor VIIa administration and when is the timing of administration and neither the appropriate dose nor the thrombotic pathophysiology are completely known (Spinella *et al.*, 2008). Hence this study was designed to further evaluate the clinical usefulness of rFVIIa in off label settings.

The Sequential Organ Failure Assessment (SOFA) score is a simple and objective score that allows estimation on the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurology) (Ferreira *et al.*, 2001). It is convenient to calculate by using clinical and laboratory data that are routinely available. The usefulness of the score has been previously validated in large cohorts of critically ill patients (Moreno *et al.*, 1999; Vincent *et al.*, 1996). The study by Alan in the Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation, noted that the SOFA score functions with fair to good accuracy for predicting in-hospital mortality.They also suggested that SOFA score is an acceptable method for risk stratification and prognosis and can be useful as measurement in clinical and research settings (Jones *et al.*, 2009).

MATERIAL AND METHOD:

i) Research tool

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This study was approved by the human ethics committee of HUSM (Approval number:

USM/JEPeM/16120535b). The patient's medical records were traced and the data of those who fulfilled the inclusion and exclusion criteria were taken using self-developed research proforma (appendix 1). Causes of massive bleeding, the laboratory investigations, SOFA score and clinical outcome of patients treated with and without rFVIIa during massive bleeding were explored. Laboratory investigations were traced from the clinical records and computerized hospital system for hematology results which is Lis Hematologi. For the SOFA Score, it was calculated according to the table given (appendix 1). Clinical outcome of thromboembolic complication including myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis, and the mortality of the patients were looked for from the clinical records. Further information regarding the total blood and blood product used were traced from the clinical records and Mytransfusi system, a computerized blood bank system used in HUSM.

ii) Sampling method

We conducted a retrospective case control analysis in Hospital Universiti Sains Malaysia KubangKerian, Kelantan from the year 2013 to 2016. About 110 patients had received rFVIIa in the 6 years duration. 70 patients who fulfilled the inclusion and exclusion criteria were selected as the case group. Out of 230 cases of massive bleeding throughout the same period, 70 case were chosen as control group via simple random sampling using computer software. Both the control and case group were matched according to the causes of the massive bleeding.

iii) Inclusion and exclusion criteria

For the case group, the data of patients who had received rFVIIa from the year 2013 to 2018, were obtained from the pharmacy department. The patients who are above 18 years old, presented with massive bleeding, admitted to the ward more than 24 hours and received recombinant FVIIa were included in the study. All subjects who met the inclusion and exclusion criteria were recruited. For the control group, patients who received more than 4 PC or had Massive Transfusion Protocol activated were traced from blood bank record. Those age 18 years old and above, presented with massive bleeding, did not receive recombinant FVIIa and admission to the ward more than 24 hours were included. Patients with haemophilia or congenital bleeding disorder, patients on anticoagulant and those with inadequate documentation were excluded from the study. The demographic data, laboratory investigations and clinical outcome of the patients are analysed. The causes of massive bleeding were matched among the group.

iv) Data Analysis

Descriptive statistics were examined for their frequencies and percentage distributions for categorical variables, while continuous data were presented as mean (SD) or median (IQR) based on their normality distribution. The conditional regression analysis for matched data for both univariable and multivariable analysis was analysed by using Cox proportional hazard model. Interaction was checked and adjusted for confounding factors. A p-value of < 0.05 is considered statistically significant. Data were analysed using IBM SPSS Statistics V24 under IBM Corporation, New York.

RESULT:

i) Demographic Data

The demographic data of the case group, patients who receives rFVIIa and the control group, patients who do not receive rFVIIa in massive bleeding were matched according to the causes of massive bleeding. Seventy patients were chosen for each group of case and control in patients with massive bleeding in Hospital Universiti Sains Malaysia between the year 2013 and 2018. The details were shown in Table 1. Mean age$\pm$ SD for the case and control group were45.89$\pm$15.64 and 47.34$\pm$17.37. The number of male patients in the case group was 38 (54.3%) and female was 32 (45.7%). The control group has 33 (47.1%) male patients and 37 (52.9%) female patients. There was no significant difference in the mean age and the percentage of gender in both groups. The causes of bleeding were grouped

based on medical and surgical causes. The primary cause for giving rFVIIa in treating massive bleeding was medical causes (n=30, 42.9%) which involved acute pulmonary haemorrhage and sepsis. This was followed by surgical causes (n=40, 57.1%), which include upper gastrointestinal bleeding, lower gastrointestinal bleeding, neurosurgeries trauma and obstetric causes.

Table I: Demographic Data and Causes of Massive Bleeding

Variables	**Case** (n=70)	**Control** (n=70)	**Crude OR** [a]	**Adjusted OR** [b]
Patient Demographics	n (%)	n (%)	(95% CI)	(95% CI)
Age	45.89 ±15.64[c]	47.34 ±17.37[c]	1.00 (0.98-1.02)	
Gender				
Male	38 (54.3%)	33 (47.1%)	1.15(0.72-1.85)	
Female	32 (45.7%)	37 (52.9%)	Reference	

[a] Simple conditional logistic regression was performed [b] Multiple conditional logistic regression was performed.[c] Data was presented as mean ± standard deviation *significant value p < 0.05

ii) Laboratory Investigation

The pre hemoglobin level for the group receiving rFVIIa was 7.51±2.04 g/dL and 6.92±2.02 g/dL in the control group and post hemoglobin level were noted 9.24±2.02 g/dL in the case group and 9.40 ±1.69 g/dL in the control group. The median for Pre PT, Pre APTT, Pre INR level for the case group were 17.40 (7.13) sec, 49.45 (19.60) sec, and 1.43 (0.80) and 20.70 (11.60) sec, 51.00 (35.00) sec and 1.81 (1.30) for the control group. The Post PT, Post APTT and Post INR median was 13.60 (5.70) sec, 42.50 (13.60) sec and 1.07 (0.56) for the case group and 16.50 (4.20) sec, 44.00 (19.40) sec and 1.37 (0.49) for the control group. There was no significant difference between the groups in univariate and multivariate analysis.

For the SOFA score, case group showed a higher mean score of 8.44±3.64 then the control group which was 6.54±3.62 with the odds of 1.07 (crude OR=1.07, 95% CI) times higher in case group compared to control group (p = 0.035).

Laboratory investigation during and after massive bleeding between the case and control were analysed and compared using paired t-test. Table 2 shows the significant increase in the hemoglobin level of both groups with 7.51±2.04 g/dL to 9.24±2.02 g/dL (p<0.001) in the case group and 6.92±2.02 g/L to 9.40±1.69 g/dL (p<0.001) in the control group.

There was significant reduction in the coagulation profile of both the case and control group with the PT 17.40 (7.13) sec to 13.60 (5.70) sec (p<0.001) in the case group and 20.70 (11.60) sec to 16.50 (4.20) sec (p<0.001) in control group, aPTT reduced from 49.45 (19.60) sec to 42.50 (13.60) sec (p<0.001) in the case group and 51.00 (35.00) sec to 44.00 (19.40) sec (p<0.001) in control group and INR improved from 1.43 (0.80) to 1.07 (0.56) (p<0.001) in case group and 1.81 (1.30) to 1.37 (0.49) (p<0.001) in case group.

Corresponding Author's: Dr.Syahirah Binti Mohamed Yusoff

Table II: Comparison of laboratory parameters in both groups during and after massive bleeding and SOFA Score

Variables	**Case** (n=70) Median (IQR)		**Control** (n=70) Median (IQR)		**Crude OR**[a] (95% CI)		**Adjusted OR** [b] (95% CI)	
Lab Ix	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Hb level	7.51 ±2.04[c]	9.24 ±2.02[c]	6.92 ±2.02[c]	9.40 ±1.69[c]	1.07 (0.96-1.21)	0.98 (0.86-1.11)	1.06 (0.94-1.20)	
P value[d]	<0.001		<0.001					
PT	17.40 (7.13)	13.60 (5.70)	20.70 (11.60)	16.50 (4.20)	0.99 (0.97-1.00)	0.98 (0.95-1.02)	0.99 (0.96-1.02	
P value[e]	<0.001		<0.001					
APTT	49.45 (19.60)	42.50 (13.60)	51.00 (35.00)	44.00 (19.40)	1.00	1.00		
P value[e]	<0.001		<0.001					
INR	1.43 (0.80)	1.07 (0.56)	1.81 (1.30)	1.37 (0.49)	0.83 (0.66-1.04)	0.91 (0.72-1.15)	1.01 (0.67-1.53)	
P value[e]	<0.001		<0.001					
SOFA score	8.44±3.64[c]		6.54±3.62[c]		1.07(1.00-1.14)*		1.07(1.00-1.13)*	

[a] Simple conditional logistic regression was performed [b] Multiple conditional logistic regression was performed.[c] Data presented as mean ± standard deviation [d]Paired sample *t*-test was performed [e] Wilcoxon Signed Rank test was performed*significant value p < 0.05 ; Hb, haemoglobin; INR, international normalized ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time.

iii) Clinical outcome

Table III shows the clinical outcome of the case and control groups. Thromboembolic complication was seen in the case group with one patient developed myocardial infarction (1.4%) and one patient developed stroke (1.4%). No thromboembolic complication were reported in the control. However when analysed by independent t-test there was no significant difference noted.

Corresponding Author's: Dr.Syahirah Binti Mohamed Yusoff

Percentage of mortality of the case and control group were taken at 24 hour and at Day 30 post massive bleeding. The number of patients who died at 24 hour for the case group was 12 (17%) and 3 (4.30%) in the control group. There was significance difference between the two groups with case group have higher mortality at 24 hour than the control group. There was no difference of the mortality of day 30 between the groups (41.4% vs 54.3%, p=0.176).

Total blood product requirement were compared between the groups. Mean number of red blood cells used was 4.50±5.00 for the case group and 6.69+5.58 for the control with significant difference (p=0.016). There was no significant difference for the fresh frozen plasma and platelet usage for both groups. For number of cryoprecipitate used, the mean was 4.33±5.23 for the case group and 6.86+7.45 for the control group with significant difference (p=0.022).

Separate analysis was done for the requirement of blood product in the case group. There is significant reduction in all the blood and blood product after initial dose of rFVIIa. Prior to the rFVIIa administration, the patients had received median of 2 units of PRBCs, 4 units of FFP, 4 units of PLT concentrate and 2units of cryoprecipitate. As shown in Table 4, the number of transfusions decreased significantly after the administration of rFVIIa (p<0.001).

Table III: Clinical outcome

Variables	**Case**	**Control**	
Thromboembolic complication	No of Patients (%)	No of Patients (%)	P value
Myocardial infarction	1 (1.4%)	0 (0 %)	0.496
Stroke	1 (1.4%)	0 (0 %)	
Pulmonary embolism	0 (0 %)	0 (0 %)	
DVT	0 (0 %)	0 (0 %)	
Mortality			
24-hr Mortality	12 (17%)	3 (4.30%)	0.033*
30- Day Mortality	29 (41.4%)	38 (54.3%)	0.176
Total blood product requirement			
Red blood cells	4.50±5.00[b]	6.69±5.58[b]	0.016*

FFP	5.41±4.01[b]	6.63±5.49[b]	0.137
Platelet	5.17±4.18[b]	4.94±5.46[b]	0.781
Cryoprecipitate	4.33±5.23[b]	6.86±7.45[b]	0.022 *

[a] Chi-square test was performed [b] Data was presented as mean ± standard deviation using independent t-test * significant value at p <0.05 ; DVT, deep vein thrombosis.

Table IV: Blood transfusion requirement before and after initial dose of rFVIIa.

Variables	**Pre**	**Post**	
Total blood product requirement	Median (IQR)	Median (IQR)	P value
Red blood cells	2.00 (3.00)	1.00 (2.00)	<0.001
Plasma	4.00 (0.00)	0.00 (4.00)	<0.001
Platelet	4.00 (3.00)	1.00 (4.00)	<0.001
Cryoprecipitate	2.00 (6.00)	0.00 (4.00)	<0.001

Values expressed as median (IQR) using Wilcoxon Signed Rank test

iv) Associatedfactors (demographic data, SOFA score and clinical outcomes) of the patients treated with and without rFVIIa and the overall survival.
Univariate and multivariate analysis were done between the associated factors and the survival of the patient. In univariate analysis , increase in one unit of median Pre Pt, Post PT, Post APTT, Post INR, red blood cell, croprecipitate and SOFA Score in the case group and increase in one unit of Post PT, Post APTT , Pre INR ,fresh frozen plasma, platelet and cryoprecipitate were associated with death. However after adjusting the laboratory investigations, only the mean number of red blood cells used (adj OR=0.75 95% CI 0.62-0.91, p=0.003) and SOFA Score (adj OR=1.22 95% CI 1.10-1.36, p<0.001) were noted to have significant value in the case group and the mean platelet usage (adj OR=1.15 95% CI 1.01-1.32, p=0.041) in the control group.

The Sofa Score were categorized, and compared between case and control groups. Better survival were noted in both groups with lower SOFA Score, Sofa Score of 0-6 (Crude OR 0.20 95% CI 0.08-0.53, p=0.001) (Crude OR 0.23 95% CI 0.09-0.62, p=0.001) and for the category 7-12 (Crude OR 0.31 95% CI 0.14-0.66, p=0.001) (Crude OR 0.37 95% CI 0.14-0.98, p=0.001) in both case control.

Further analysis of the SOFA score by categories and the survival of the patients for medical and surgical in both groups revealed that the surgical patients in the case group have better survival with lower SOFA Score, 0 to 6 Sofa Score, (Crude OR 0.04 95% CI 0.01-0.26, p=0.001) and 7-12 Sofa Score (Crude OR 0.08 95% CI 0.02-0.34, p=0.001)

Corresponding Author's: Dr.Syahirah Binti Mohamed Yusoff

compared to the surgical patients in control group. Not much differences noted in the medical patients in both groups.

Table V: Predictors of death according to variables

Variables	**Case (n=70)** Median (IQR)		**Control (n=70)** Median (IQR)		**Crude OR[a]** (95% CI)		**Adjusted OR [b]** (95% CI)	
	Survive n=29 (41.4%)	Died n=41 (58.6%)	Survive n=38 (54.3%)	Died n=32 (45.7%)	Case	Control	Case	Control
Age	46.07 ±14.86[c]	45.76 ±16.35[c]	45.21 ±17.53[c]	48.69 ±17.37	1.00 (0.98-1.02)	1.01 (0.98-1.03)		
Gender Male Female	14(48.3%) 15(51.7%)	24(58.5%) 17(41.5%)	17(44.7%) 21(55.3%)	16(50.0%) 16(50.0%)	1.21(0.65-2.25) REF	1.36(0.68-2.73) REF		
Pre Hb	7.91 ±2.26[c]	7.25 ±1.81[c]	7.20 ±2.06[c]	6.63 ±1.88[c]	0.90 (0.78-1.08)	0.88 (0.74-1.05)		
Post Hb	9.45±1.90	9.08±1.08	9.41±1.67	9.39±1.76	0.92 (0.78-1.08)	0.97 (0.78-1.22)		
Pre PT	16.10 (6.15)	17.60 (8.23)	18.45 (8.45)	24.0 (12.65)	1.02 (1.00-1.04) *	1.01 (1.00-1.02)		
Post PT	13.30 (4.95)	13.85 (7.80)	15.65 (3.55)	18.7 (12.00)	1.06 (1.03-1.09) *	1.10 (1.05-1.15) *		
Pre APTT	48.80	51.30	58.45 (19.25)	49.40 (27.72)	1.00	1.00		

Corresponding Author's: Dr.Syahirah Binti Mohamed Yusoff

	(18.80)	(19.25)			(0.98-1.01)	(1.00-1.01)		
Post APTT	39.30 (13.75)	43.75 (13.48)	41.4 (14.43)	47.40 (49.6)	1.02 (1.01-1.03) **	0.83 (0.66-1.04) **		
Pre INR	1.35 (0.74)	1.47 (0.82)	1.55 (0.91)	2.04 (1.34)	1.31 (1.00-1.73)	1.11 (1.01-1.23)*		
Post INR	1.02 (0.50)	1.21 (0.81)	1.27 (0.35)	1.40 (0.72)	1.55 (1.23-1.94) **	1.07 (0.93-1.22)		
PC	4.00 (6.50)	2.00 (3.00)	4.00 (5.00)	5.00 (7.75)	0.87 (0.79-0.97) **	1.07 (1.01-1.13) **	0.75 (0.62-0.91) **	
FFP	4.00 (5.00)	4.00 (4.00)	4.00 (8.00)	7.00 (8.00)	0.97 (0.89-1.05)	1.12 (1.05-1.20) *		
Platelet	4.00 (6.00)	4.00 (6.00)	4.00 (7.25)	4.00 (8.00)	0.97 (0.90-1.05)	1.12 (1.05-1.20) *		1.15 (1.01-1.32) *
Cryo	4.00 (10.00)	2.00 (5.50)	4.00 (12.00)	6.00 (15.00)	0.96 (0.90-1.02) **	1.09 (1.03-1.14) **		
SOFA Score	6.62±2.97[c]	9.73±3.55[c]	5.32±3.04[c]	8.00±3.78[c]	1.18 (1.08-1.29) **	1.15 (1.05-1.27)	1.22 (1.10-1.36) **	

[a] Simple conditional logistic regression was performed [b] Multiple conditional logistic regression was performed.[c] Data presented as mean ± standard deviation *significant value $p < 0.05$; Hb, haemoglobin; INR, international normalized ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time.

Table VI: Category of SOFA score in survivors and non survivors in both groups

SOFA Score	Case n (%)		Control n (%)		Crude OR [a] (95% CI)	
	Survive 29 (41.4)	Died 41 (58.6)	Survive 38 (54.3)	Died 32 (45.7)	Case	Control
0-6	12 (17.1)	8 (11.4)	26 (37.2)	13 (18.6)	0.20 (0.08-0.53)*	0.23 (0.09-0.62) *
7-12	17 (24.3)	23 (32.9)	11 (15.7)	13 (18.6)	0.31 (0.14-0.66) *	0.37 (0.14-0.98) *
13-18	0 (0)	10 (14.3)	1 (1.4)	6 (8.5)	REF	REF
19-24	0 (0)	0 (0)	0 (0)	0 (0)		

[a] Simple conditional logistic regression was performed

Table VII: Survival rate of medical and surgical patients according to the SOFA Score.

SOFA score	Medical (n=60) Survival n (%) n=21 (35)		Surgical (n=80) Survival n (%) n=46 (57.5)		Crude OR[a] (95% CI)			
					Medical		Surgical	
	Case	Control	Case	Control	Case	Control	Case	Control
0 - 6	4 (6.8)	8 (13.3)	8 (10)	18 (22.5)	0.61 (0.91-2.01)	7.35 (1.45-37.32)*	0.04 (0.01-0.26)*	0.08 (0.06-1.45)
7 - 12	2 (3.3)	6 (10)	15 (18.7)	5 (6.3)	1.90 (0.68-5.33)	1.20 (0.32-4.65)	0.08 (0.02-0.34)*	1.33(0.27-6.63)

Corresponding Author's: Dr.Syahirah Binti Mohamed Yusoff

13 - 18	0 (0)	1(1.6)	0 (0)	0 (0)	REF	REF	REF	REF
19 - 24	0 (0)	0 (0)	0 (0)	0 (0)				

[α] Simple conditional logistic regression was performed *significant value $p < 0.05$

DISCUSSION:

A total of 140 patients were analysed, 70 were on the use of rFVIIa in massive bleeding, and another 70 patients were matched as the control group. The study were conducted in two main clinical situations which was medical and surgical causes of massive bleeding. The main outcomes were mortality in 24 hour and 30 day, blood and blood product transfusion requirements, as well as thromboembolic adverse events. The associated factors of the groups with the overall survival were identified.

In this study, the age of recipients range from 18 to 84 years old with no significant difference between the groups (p=0.603). There was also no significant difference in terms of gender. There were about 30 (42.9%) medical patients and 40 (57.1%) were surgical patients who received rFVIIa. The case and control were matched according to the causes of massive bleeding to reduce the bias between the groups.

The initial laboratory investigation, Pre Hb, Pre PT, Pre aPTT and Pre INR were about the same between the groups with no significant difference. This is also an important factor to remove the bias among the groups. The Pre Hb level of both the groups are low which was less than 8g/dL, corresponds with the European guideline on management of major bleeding and coagulopathy following trauma: fifth edition, noted that initial low Hb can be considered as an indicator for severe bleeding associated with coagulopathy(Spahn *et al.*, 2019). It is also one of the predictive criteria for massive transfusion using the trauma-associated severe haemorrhage (TASH) (Maegele, 2009) and Vandromme scores (Vandromme *et al.*, 2011).

Pt, APPT and INR termed as standard laboratory coagulation tests were encouraged by numerous guidelines and publications to be used in the diagnosis of coagulopathy during massive bleeding (Liumbruno *et al.*, 2011; "Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies: An Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies," 2006). The presence of hemorrhage along with coagulopathy, with prolong PT, APTT and INR seen in the both case and control groups indicates for damage control resuscitation (Cannon *et al.*, 2017). Significant improvement of all laboratory markers (Hb, PT, aPTT, INR) were observed in both groups post massive bleeding ($p<0.001$). This shows active management of massive bleeding were done in both groups. The guidelines from the Eastern Association for the Surgery of Trauma recommend the transfusion of equal amounts of RBC, plasma and platelets during the early, empiric phase of resuscitation (Cannon *et al.*, 2017). However, other authors, mainly in Europe, strongly support the use of factor concentrate as the first line of initial coagulation resuscitation in patients with significant bleeding. Soliman et al., noted that the activated partial thromboplastin time (aPTT) for refractory bleeding in cardiac surgery patients was 45.53± 9.81 and significantly reduced to 41.25 ± 8.82 after rFVIIa was given (Soliman and Belghith, 2012). It was also agreed by Palmason*et al.*, where there was correction of coagulation profile in term of shortening of prothrombin time post administration rFVIIa(PALMASON *et al.*, 2012) .Significant marked reduction of INR was noted after treatment with rFVIIa in patients with massive blood loss in cardiac surgery (Karkouti *et al.*, 2005).

Univariate analysis of the associated factors for overall survival noted significant differences in the Pre PT, Post PT, Post APTT and Post INR of the patients who survived in the case group. They have lower values than the non survivors. Recombinant factor VIIa have the ability to rapidly correct the

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coagulation profile while avoiding volume overload. The advantages of rFVIIa over blood products include its small infusion volume, room temperature storage, rapid correction of coagulation parameters, and safety profile (eg: absence of transfusion reaction and blood borne pathogens). These characteristics have led to extensive off-label use of rFVIIa as an adjunct in the management of coagulopathy in a wide and varied number of subpopulations (Lombardo *et al.*, 2018).

SOFA Score is a reliable and accurate assessment of the severity of a patient's illness. It was found to be applicable for both septic as well as nonseptic patients (Vincent *et al.*, 1996). However usage of rFVIIa in those with massive hemorrhage as a last resort has noted to be ineffective (PALMASON *et al.*, 2012). It was proven in this study as the case group which has significant higher mean SOFA Score than the control group, (p= 0.035) has higher 24 hour mortality rate than the control group (17% vs 4.3%, p=0.033). The higher mean SOFA score in case group shows that more critically ill patients were given rFVIIa then the control group in massive bleeding. However when the 24 hour mortality rate is compared to the study of Payen et al., in 'Reduced mortality by meeting guideline criteria before using recombinant activated factor VII in severe trauma patients with massive bleeding', the mortality rate in 24 hour were similar (17%) (Payen *et al.*, 2016). Clark et al, examining rFVIIa as a "last-ditch" in patients with massive haemorrhage, noted high mortality rates (1-day and 7-day mortality 40% and 70% respectively) and concluded that last-ditch rFVIIa therapy is ineffective in patients who do not respond to extended conventional treatment (Clark *et al.*, 2004).

Mean SOFA Score was one of the associated factors for overall survival in the case group with significant differences noted in both survivors and non survivors (adj OR=1.22 95%CI 1.10-1.36, p<0.001). This finding is similar with the study of Bowles in predicting response to rFVIIa in non-hemophiliac patients with severe hemorrhage, whereby lower SOFA score was noted in the survivors then the non survivors (Bowles *et al.*, 2006). Moreno et al:, demonstrated a strong correlation of SOFA score with the mortality outcome (Moreno *et al.*, 1999).

Further analysis was done by categorising the SOFA Score in medical and surgical causes of massive bleeding in both groups and determine the association with the overall survival. Surprisingly, it shows that the surgical patients in the case group with lower SOFA score of less than 13, had better survival then the medical patients (p. This raise the hypothesis of the benefit of giving rFVIIa in surgical patients with lower score, whereby the rFVIIa treatment should be considered early , before the onset of organ failure (Bowles *et al.*, 2006) . High mortality was noted with SOFA Score of more than 12 and probability of less beneficial effect in giving rFVIIa in patients with SOFA score more than 13. Patients with medical causes of massive bleeding has less survival probably because most of them are hematological malignancy patients who are post chemotheraphy, pancytopenia and followed by massive bleeding. They are more vulnerable and already have poor premorbid condition.

The potential for thromboembolic complications with the usage of rFVIIa has been demonstrated in several trials and retrospective analyses (Diringer *et al.*, 2010; Hsia *et al.*, 2008; Roberts *et al.*, 2004). Levi and coworkers reported an increase in arterial thrombotic adverse events among all published RCTs investigating off-label use of rFVIIa (5.5 vs 3.2%, p=0.003) (Levi *et al.*, 2010). Previous analyses of voluntary reports to the FDA Adverse Event Reporting System identified deep venous thrombosis, ischemic cerebrovascular accident, and myocardial infarction as the most common adverse events associated with rFVIIa use (Aledort, 2004; O'Connell *et al.*, 2006). Gill et al reported there were increases in thromboembolic adverse events, particularly stroke, in the rFVIIa groups, although they did not reach statistical significance (Gill *et al.*, 2009). In our study, there were one case of stroke and one case of pulmonary embolism in the case group, and no cases were reported in the control group (2.8% vs 0%, p=0.496) which is much lower compared to other studies. There was no significant difference noted among the groups hence reducing the concern about potential harms with off label application. A phase II randomized controlled trial

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of the use of rFVIIa/placebo in 277 patients with haemorrhage after blunt and penetrating trauma, supports our result as there also no difference in thromboembolic events between treatment and control group in the study (Rizoli *et al.*, 2006). There was also no association of the thromboembolic events with the overall survival noted.

Another important finding in our study was the significant reduction of allogenic blood transfusion whereby the packed cell (p=0.016) and the cryoprecipitate (p=0.022) usage were reduced in the case group when compared to the control group. Gill and colleagues reported a placebo-controlled RCT in which patients with bleeding episodes after cardiovascular surgery were randomly assigned to receive a single dose of rFVIIa at 40 mcg/kg (n = 35) or 80 mcg/kg (n = 69) versus placebo (n = 68). Significant decreases in the need for reoperation and allogeneic blood transfusions were seen in the groups that received rFVIIa, but there were no differences in mortality (Gill *et al.*, 2009). This results were similar with our study where there was reduction in the allogenic blood transfusion but there were no differences in the 30 day mortality of the groups. Separate analysis were done for the blood requirement for the patients that received rFVIIa and the result shows that there was significant reduction in the usage of all blood and blood products in the case group (p<0.001). Karkouti et al, also reported regarding the reduction of the number units of blood and blood product transfused in the patients undergoing cardiac surgery with massive blood loss receiving rFVIIa(Karkouti *et al.*, 2005). This is an important finding, as massive transfusion can further lead to blood loss by increasing hydrostatic pressure on the clots, an aggravation of hypothermia, and a further dilution of coagulation factors which cause coagulopathy. The mortality rate in patients receiving massive transfusion is high about 19 percent to 45 percent (Riskin *et al.*, 2009).

Study limitation

This was a single centre study, a broader range of patients could be analysed if other centres are also included. The result should be interpreted carefully and cannot be generalised to other settings. This was a retrospective study, which has the possibility of missing cases and data. The amount of blood loss and time of rFVIIa given should be taken into account so that more appropriate result could be interpreted and criteria on off label usage of rFVIIa could be developed by local experience.

CONCLUSION:

This study indicates the benefits of intervention with rFVIIa for management of massive bleeding in surgical patients with lower SOFA Score. The survival rate noted to be higher in this patients when compared to the control group and medical causes of massive bleeding. A reduced in the amount of transfusion requirement observed in the case group hence reducing the possible adverse effect of massive transfusion. Improvement of coagulation profiles were observed in both groups indicates appropriate management given in both groups. There was no significant difference in thromboembolic complication between the groups hence safety profile of rFVIIa were proven. This study stress the importance of SOFA Score in prediction of overall survival of the patients.

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Conflicts of Interest:

No potential conflict of interest declared.

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