RECOMBINANT FACTOR VIIA IN MASSIVE BLEEDING AT HOSPITAL UNIVERSITI SAINS MALAYSIA

BY,

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DISCLAIMER

I declare that this dissertation records the results of the study performed by me and that it is my own composition.

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Dr Syahirah Binti Mohamed Yusoff

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

rFVIIa	Recombinant Factor VII Activated
SOFA	Sequential Organ Failure Assessment
Hb	Haemoglobin
PT	Prothrombin Time
aPTT	Activated Partial Thromboplastin Time
INR	International Normalized Ratio
DVT	Deep Vein Thrombosis
PRBC	Packed Red Blood Cell
FFP	Fresh Frozen Plasma
SD	Standard Deviation
IQR	Inter Quartile Range
SPSS	Statistical Package For The Social Sciences
CI	Confidence Interval
REF	Reference
OR	Odds Ratio
ICU	Intensive Care Unit
JEPeM	Jawatankuasa Etika Penyelidikan (Manusia)
USM	Universiti Sains Malaysia
HUSM	Hospital Universiti Sains Malaysia

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ABSTRAK

PENGENALAN: Pendarahan masif merupakan salah satu punca mortaliti dan morbiditi yang dapat dielakkan. Resusitasi hemostasis masif mempunyai manfaat dan risiko tersendiri. Kajian ini bertujuan untuk melihat perbezaan dan hasil daripada pesakit bukan hemofilia yang dirawat dengan dan tanpa rFVIIa semasa pendarahan masif di Hospital Universiti Sains Malaysia (HUSM) dalam jangkamasa enam tahun.

KAEDAH: Kami menjalankan analisis retrospektif kohort di Hospital Universiti Sains Malaysia Kubang Kerian, Kelantan dari tahun 2013 ke 2018. Seramai 140 pesakit yang memenuhi syarat kemasukan dan pengecualian telah dipilih sebagai subjek kajian dan dibahagikan kepada kumpulan yang menerima rawatan rFVIIa dan tidak menerima rawatan rFVIIa. Keputusan makmal (tahap hemoglobin, PT, aPTT dan INR), *Sequential Organ Failure Assessment* (SOFA) dan hasil klinikal pesakit telah dianalisis.

KEPUTUSAN: Terdapat 40 (57.1%) pesakit pembedahan yang menerima rFVIIa. Perbandingan kelangsungan hidup 30 hari dalam pendarahan masif disebabkan oleh pembedahan dan perubatan menunjukkan terdapat kecenderungan menunjukkan kadar kelangsungan hidup yang lebih tinggi oleh penyebab pembedahan terutamanya pada skor SOFA yang lebih rendah. Selain itu, dalam sebab pembedahan, kadar kelangsungan hidup serupa (57.5%) walaupun terdapat perbezaan skor SOFA min (p=0.006). Apabila kita membandingkan pendarahan masif disebabkan oleh perubatan, kumpulan yang menerima rFVIIa mempunyai hasil yang lebih buruk (p=0.003). Pengurangan keperluan produk darah juga dicatat dalam kumpulan rawatan.

KESIMPULAN: Kajian ini menunjukkan faedah intervensi dengan rFVIIa untuk pesakit pendarahan masif disebabkan pembedahan dengan skor SOFA yang lebih rendah. Selain itu, hasil kajian menunjukkan bahawa tidak ada manfaat dalam penggunaan rFVIIa untuk mengawal pendarahan masif disebabkan oleh sebab-sebab perubatan.

(243 patah perkataan)

Kata kunci: Pendarahan masif, recombinant factor VIIa, skor SOFA, produk darah

ABSTRACT

INTRODUCTION: Massive bleeding is a salvageable cause of mortality and morbidity. Vigorous haemostatic resuscitation carries its own benefit and risk. This study aims to explore the indications and outcomes of non-haemophilia patients treated with and without rFVIIa during massive bleeding in Hospital Universiti Sains Malaysia (HUSM) over a 6-year-period.

METHODS: A retrospective cohort analysis from year 2013 to 2018 was conducted. One hundred forty massive bleeding patients who were treated with and without rFVIIa during massive bleeding and fulfilled the inclusion and exclusion criteria were recruited and evaluated. Their laboratory investigations (haemoglobin, PT, aPTT and INR), Sequential Organ Failure Assessment (SOFA) score and clinical outcomes were explored.

RESULTS: The primary cause for rFVIIa administration was surgical causes (57.1%). Comparison of 30 day survival within surgical and medical causes of massive bleeding showed a higher survival rate among surgical causes especially in lower SOFA score. Besides that, in surgical causes, the survival rate is similar (57.5%) despite significant difference of the mean SOFA score (p=0.006). When we compare the medical causes of massive bleeding the treatment group have poorer outcome (p=0.003). Reduction of blood product requirement were also noted in the treatment group.

CONCLUSION: rFVIIa may be more beneficial to be used in surgical causes of massive bleeding, especially when patients still have lower SOFA score. Besides, no benefit of rFVIIa was shown among medical causes of bleeding, regardless of the SOFA score.

(232 words)

Keywords: Massive bleeding, rFVIIa, SOFA Score, blood product

CHAPTER ONE

INTRODUCTION

1.1 Overview

This chapter covers some brief introduction, pathophysiology and management of massive bleeding and off label usage of recombinant factor VIIa in clinical settings. This chapter also highlights the problem statements and objectives of the study.

1.2 Background of study

Massive bleeding can be defined as blood loss exceeding one total body volume in 24 hours, 50% blood loss in 3 hours, bleeding rate of 150ml/min or more, and massive bleeding requiring blood component transfusion (Irita, 2011). Massive transfusion is defined as more than 10 units of red cells are required in 24 hours or blood loss of more than 1 to 1.5 fold of body volume (Meißner and Schlenke, 2012). Other definitions are transfusion of more than 4 packed red cells in 1 hour, anticipated the continued need for blood and blood product support and replacement of more than 50% of the total blood volume with blood products within 3 hours (Pham and Shaz, 2013).

Massive bleeding is a medical emergency that requires urgent diagnosis and treatment because it can cause additional organ damage and death. It was reported that survival could be improved in trauma patients with major haemorrhage in need of emergency surgery if the time frame between injury and operating theatre's admission is reduced (Spahn *et al.*, 2019). This can be minimised during the acute episode by rapid diagnosis and control of major bleeding. Massive bleeding also leads to the presence of anaemia which reduces primary haemostasis by impairing platelet adhesion and aggregation (Pham and Shaz, 2013). Tissue factor released from tissue damage during trauma or surgery stimulates the coagulation pathway systematically resulting in massive coagulopathy which contributes to disseminated intravascular coagulopathy.

Hypoperfusion from major bleeding induces the expression of thrombomodulin in endothelial cells and this complex of thrombin-thrombomodulin activates protein C which reduces the activation of the fibrinolysis inhibitor (TAFI). They further restrict coagulation by inhibiting factor V and VIII thereby enhancing fibrinolysis through the depletion of plasminogen activator inhibitor (PAI) (Meißner and Schlenke, 2012).

It is shown that the mortality rate in massive bleeding increases with increasing blood loss in both emergency and elective cases (Irita, 2011). Serial monitoring of the laboratory investigations is important as initial low Hb level helps in diagnosing severe bleeding associated with coagulopathy (Spahn *et al.*, 2019). Trauma-associated severe haemorrhage (TASH) and Vandromme scores uses Hb level as the predictive criteria in massive transfusion (Brockamp *et al.*, 2012). Schlimp et al (2013), demonstrated strong relationship between fibrinogen and haemoglobin levels. It was noted that major trauma patients with Hb < 12 g/dL had 74% low fibrinogen (< 200mmol/L), Hb < 10 had 89% low fibrinogen and Hb < 8 had 93% low fibrinogen level. They propose that fibrinogen level can be estimated by this bedside tests (Schlimp *et al.*, 2013). In addition, fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) administration could also be driven by an INR value of 1.5 (David *et al.*, 2012).

The Sequential Organ Failure Assessment (SOFA) score is helpful to stratify and compare patients in clinical trials. It is important to quantify the degree of organ dysfunction or failure present on admission. Furthermore, it can help in monitoring the degree of organ dysfunction and mortality outcome developed during an ICU stay (Hwang *et al.*, 2012). Six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic) were assessed as an objective score for the severity of organ dysfunction (Jain *et al.*, 2016). It uses clinical and laboratory data that are routinely done hence can be calculated at the bedside. Validation of the score had been done via large

cohort study involving critically ill patients (Payen *et al.*, 2016). The mean SOFA score also used to predict the prognosis and mortality rate (Spahn *et al.*, 2019).

The conventional concept of resuscitation in acutely bleeding patients was aggressive fluid administration to restoring intravascular blood volume. Nevertheless, this approach can further lead to increase hydrostatic pressure on the clots, worsening hypothermia, and dilutional coagulopathy (Chatrath *et al.*, 2015). Few studies in both non-critically and critically ill patients demonstrated that aggressive fluid resuscitation may cause further harm by reducing the renal blood flow velocity and renal cortical tissue perfusion, hyperchloraemic acidosis, increasing the incidence of kidney injury or even reduced survival (Lobo and Awad, 2014). Colloid solutions noted to cause transient intravascular expansion compared to crystalloid solutions. It may also cause adverse effects by decreasing serum ionized calcium, decrease circulating levels of immunoglobulins, and compromising the extracellular fluid volume (Vishwakarma *et al.*, 2015).

A study by Tanaka, indicates that improvement of microcirculation and tissue oxygenation were noted with RBC transfusion independent of microcirculation and Hb level (Tanaka *et al.*, 2017). Transfusion of fresh frozen plasma (FFP), platelets, and RBC at 1:1:1 unit ratios during resuscitation, consisting of coagulation factor concentration 65% of average, 88 x 10^9 /L platelet count, and 29% haematocrit. Approximately 30% of the platelets and 10% of the RBC administered will not circulate (Kornblith *et al.*, 2014). A study by Holcomb, shows a benefit for the 1:1:1 approach in massively injured and rapidly bleeding patients. Six hundred and eighty patients with major bleeding were randomly assigned to receive 1 to 2 RBC transfusions for each FFP and platelet unit (e.g., 1:1:1 to 1:1:2 platelet to FFP to RBC). The 1:1:1 strategy was noted to have a slightly better outcome with sufficient haemostasis (86% vs. 78%) observed among them, with

fewer deaths at 24 hours (9% vs. 15%). There was no difference in overall mortality at 1 and 30 days, although at both points of time there was a pattern supporting 1:1:1. Adverse events were also similar between the groups (Holcomb *et al.*, 2015).

Recombinant factor VIIa (NovoSeven ®) is a recombinant human coagulation factor VIIa (rFVIIa), designed to promote haemostasis by triggering the coagulation cascade's extrinsic pathway. It activates the final common pathway of the coagulation cascade independent of the presence of factor VIII and factor IX. rFVIIa forms a tissue factor complex which activates coagulation factor X in the presence of calcium and phospholipids and then initiates the transformation of prothrombin into thrombin (Shetty and Ghosh, 2015). In 1999, the FDA approved rFVIIa for the treatment of episodes of spontaneous or surgical bleeding in patients with haemophilia A or B with factor VIII or factor IX inhibitors. However nowadays rFVIIa has been used in off-label settings, rapidly for the treatment or prophylaxis of bleeding in other conditions (Streiff and Cotton, 2013).

Increased usage of off-label rFVIIa by 143 fold from 2000 to 2008 were noted in the report of American Hospital. In 2008, cardiac surgery (27%), trauma (18%) and intracranial haemorrhage (ICH; 11%) were the main causes of rFVIIa in-hospital use (Logan *et al.*, 2011). Initially it was not routinely used in the management of massive bleeding. However after the first case report of its successful in controlling traumatic coagulopathy in a severely injured soldier, there was increasing off lable use of rFVIIa (Morse *et al.*, 2011). Studies have shown that more than 95% of rFVIIa in-hospital usage was off-label (Logan *et al.*, 2011). Even though this off-label use is still not proven to be associated with a survival benefit, there are literatures showing an improved outcome. Nonetheless, the effectiveness of rFVIIa as a more general haemostatic drug, whether

prophylactically or therapeutically, as well as thromboembolic events with rFVIIa use, remains unproven.

rFVIIa was not routinely used in massive bleeding during 2013-2018 because the usage is still considered off-label. The use of rFVIIa in HUSM was based on treating clinician's clinical judgement and each decision was individualized based on patient's condition. Each decision was made by the treating clinician after discussing with consultant haematologist oncall, and all the off-label use of rFVIIa need to be reported to the rFVIIa Registry in Managing Critical Bleeds in Non-Haemophilia Patients. Thus this study was conducted to explore the outcome of the usage during that period of time and provide information to the clinicians regarding the outcome hence improving further the decision making of the usage of rFVIIa especially in massive bleeding episodes.

1.3 Problem statement

This study is important as there are inadequate local data regarding the usage of rFVIIa in other clinical settings especially in massive bleeding. The result obtained will help us to further evaluate the usage of rFVIIa in off label settings hence provide the basis for the development of local guidelines. One of the biggest unknowns in the off-label use of rFVIIa is the safety profile of the drug. rFVIIa is a very potent agent and thought to predispose susceptible patients to thromboembolic complications such as stroke, myocardial infarct (MI), and deep vein thrombosis. The safety should become increasingly clearer as clinical experience encourages us to use this medication earlier and in a broader spectrum of patients. Furthermore, the effectiveness of off label usage of rFVIIa shows variable results between the studies conducted and the possible benefit of rFVIIa might be missed by usage in moribund patient and futile use in patient without massive bleeding. Proper selection of study population will provide more transparent results and avoid bias. For example in the use of rFVIIa with patients with intracranial haemorrhage, Deloughery et al. found that patients receiving rFVIIa had a higher death rate (45.7% vs. 14.3% P = 0.001) compared with matched controls. However same rate of thromboembolic complications were noted between the groups (5.7% vs. 5.7%). Regardless of the severity of the injury, the use of rFVIIa was not effective in this case control study with increased mortality risk (DeLoughery *et al.*, 2011).

SOFA score could be a useful tool as the predictor for organ dysfunction and mortality rate, however most of the study related to the score were done among ICU patients. Mahambrey et al., noted that massively transfused trauma patients has high SOFA score and high mortality rate (Mahambrey *et al.*, 2009).

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1.4 OBJECTIVES

1.4.1 General objective

To study the indications and outcomes of non-haemophilia patients treated with and without rFVIIa during massive bleeding in Hospital Universiti Sains Malaysia (HUSM).

1.4.2 Specific objectives

i. To compare the demographic characteristics, laboratory investigations (haemoglobin level and coagulation profile), SOFA score, and clinical outcomes (thromboembolic complications, mortality rate and total blood products requirement) of patients treated with and without rFVIIa during massive bleeding.

ii. To compare the difference of blood products requirement between case and control

iii. To determine the associated factors (demographic data, SOFA score and clinical outcomes) of the patients treated with rFVIIa and the overall survival.

1.4.3 Alternative Hypotheses

H_{A1}: There is a significant comparison between the laboratory investigations (haemoglobin level and coagulation profile), SOFA score, and clinical outcomes (thromboembolic complications, mortality rate and total blood products requirement) of patients treated with and without rFVIIa during massive bleeding.

H_{A2}: There is significant differences between the blood products requirement with rFVIIa treatment.

H_{A3}: There is significant association between the demographic data, SOFA score and clinical outcomes of the patients treated with rFVIIa and without rFVIIa with the overall survival

1.4.4 Null hypotheses

H_{01}: There is no significant comparison between the laboratory investigations (haemoglobin level and coagulation profile), SOFA score, and clinical outcomes (thromboembolic complications, mortality rate and total blood products requirement) of patients treated with and without rFVIIa during massive bleeding.

H_{02}: There is no significant differences between the blood products requirement with rFVIIa treatment.

H_{03}: There is no significant association between the demographic data, SOFA score and clinical outcomes of the patients treated with rFVIIa and without rFVIIa with the overall survival.

CHAPTER TWO

STUDY PROTOCOL

PROPOSAL FOR MASTER OF TRANSFUSION MEDICINE

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

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Introduction

Coagulation is a complex physiologic process involving multiple proteins and other blood components to produce the fibrin and platelet network. It is an important process that prevent excessive bleeding when injury occurs. The normal coagulation pathway starts with a vascular insult. It then causes blood vessels to vasoconstrict and releases collagen, von Willebrand factor, and tissue factor from the damaged vascular endothelium. Vasoconstriction of the vessels assists platelets migration from the vascular lumen toward the vessel wall and injury. Platelet aggregation at the site of an injury produces a temporary loose platelet plug (D'Angelo and Dutton, 2010).

The tissue factor accelerates the activation of factor VII, which in turn, activates factor IX. The cascade continues with the activation of factors VIII and X that ultimately begins the conversion of prothrombin (II) to activated thrombin (IIa), resulting in a "thrombin burst" on the surface of the platelet converting fibrinogen to fibrin (Ia). Fibrin polymerizes, forming a strong matrix over the platelet plug. The clot is stabilized when fibrin is cross-linked to factor XIIIa. (D'Angelo and Dutton, 2010). However in the case of massive bleeding which further leads to massive transfusion, the coagulation disturbances are contributed by many factors for example consumption of clotting factors at the site of injury and the dilution from the infusion of fluids, blood and blood products. In traumatic injury, there are other pathophysiology of coagulopathy associated, such as role of activated protein C, hypofibrinogenemia and fibrinolysis (Meißner and Schlenke, 2012).

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 blood loss that necessitates plasma and platelet transfusion (Irita, 2011). Massive transfusion defined as transfusion of more

than 10 units of packed red cell 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 red blood cells (RBC) in 1 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). Massive bleeding is a medical emergency requiring immediate diagnosis and treatment as it can lead to organ damage and possibly death. It is shown that the mortality rate increases with increasing blood loss in both emergency and elective cases (Irita, 2011).

The main goals are early recognition of blood loss and early resuscitation, maintenance of tissue perfusion and oxygenation by restoration of blood volume and hemoglobin, judicious use of blood component therapy and timely availability of required blood components in resuscitation to maintain hemodynamic stability and to avoid organ injury. Identification of the source and bleeding and early resuscitation have to be done simultaneously to ensure rapid control of bleeding and to restore systemic oxygen delivery.

Massive bleeding leads to the presence of anemia which reduces primary hemostasis by impairing platelet adhesion and aggregation. Besides that, tissue injury from trauma or surgery releases tissue factor locally and subsequently systematically activates coagulation pathway and results in massive consumptive coagulopathy leading to a consumptive disseminated intravascular coagulopathy. Hypoperfusion from massive bleeding cause thrombomodulin expression on endothelial cells. These thrombin-thrombomodulin complex then activates protein C which reduces the activation of thrombin-activatable fibrinolysis inhibitor (TAFI), limits the coagulation by inhibiting factor V and VIII and enhancing fibrinolysis by the depletion of plasminogen activator inhibitor (PAI) (Meißner and Schlenke, 2012).

Administration of red blood cells without additional clotting factors or platelet may cause dilutional coagulopathy and thrombocytopenia. Citrate in storage solutions causes metabolic derangement (acidosis) which further cause hemostasis impairment. Another important contributor to coagulopathy is hypothermia (temperatures below 35 °C). Factors contributing to hypothermia include infusion of cold fluids and blood and blood products, opening of coelomic cavities and decreased heat production. Hypothermia leads to decreased citrate metabolism and drug clearance and more importantly, contributes to the development of coagulopathy (Patil and Shetmahajan, 2014). It causes a reversible platelet dysfunction, alters coagulation and enhances fibrinolysis. Unfortunately, the contribution of hypothermia to the haemorrhagic diathesis may be overlooked because coagulation testing is usually performed at 37 °C.

The main and traditional concept of resuscitation in acutely bleeding trauma patients was aggressive fluid administration aimed at restoring intravascular blood volume. This approach, however, may contribute to further blood loss by increasing hydrostatic pressure on the clots, an aggravation of hypothermia, and a further dilution of coagulation factors. Resuscitation with fresh frozen plasma (FFP), platelets, and RBC at 1:1:1 unit ratios means that the actual blood being given has a coagulation factor concentration of 65 percent of normal, a platelet count of 88 x 109/L, and a hematocrit of 29 percent. Because 30 percent of the platelets and 10 percent of the RBC administered will not circulate, the effective concentrations are a plasma coagulation factor concentration of 65 percent, platelet count of 55 x 109/L, and a hematocrit of 26 percent respectively (Kornblith *et al.*, 2014). A study by Holcomb, shows a benefit for the 1:1:1 approach in massively injured and rapidly bleeding patients. Randomly assigned 680 patients with major bleeding from severe trauma to receive transfusion of 1 versus 2 units of RBC for every unit of FFP and platelets (eg: FFP to platelets to RBC

of 1:1:1 versus 1:1:2) found slightly better outcomes with the 1:1:1 approach. Patients assigned to 1:1:1 were more likely to have adequate hemostasis (86 versus 78 percent) and had fewer exsanguination deaths at 24 hours (9 versus 15 percent). Overall mortality at 1 and 30 days were not different between the groups, although there was a trend favoring 1:1:1 at both time points. Adverse events were also similar between the groups (Holcomb *et al.*, 2015).

Recombinant factor VIIa (NovoSeven®) is a recombinant human coagulation factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade. It activates the final common pathway of the coagulation cascade independent of the presence of factor VIII and factor IX. rFVIIa forms a complex with tissue factor, which in the presence of calcium and phospholipids activates coagulation factor X which then initiates the conversion of prothrombin into thrombin (O'Connell *et al.*, 2006).

The FDA approved recombinant factor VIIa (rFVIIa) (Novo Nordisk, Bagsværd, Denmark) in 1999 for treatment of spontaneous or surgical bleeding episodes in patients with hemophilia A or B who have inhibitors to factor VIII or factor IX. When first introduced, rFVIIa was used predominantly for these indications. However nowadays rFVIIa in has been used in off-label settings, rapidly for the treatment or prophylaxis of bleeding in other conditions. In the report of American hospitals, use of off-label rFVIIa increased by 143-fold from 2000 to 2008. In 2008, the top indications for in-hospital use of rFVIIa were cardiac surgery (27%), trauma (18%) and intracranial haemorrhage (ICH; 11%) (Logan *et al.*, 2011). In the haemostasis registry final report of rFVIIa use in Australia and New Zealand between 2000 and 2009, rFVIIa use reached a plateau in 2006 to 2008 with a slight decline in 2009 Similarly, the largest users in 2009 were surgery and trauma patients (Zatta *et al.*, 2014).

Randomised control trials by Mayer in 2005, 2006 and 2008, involving use of rFVIIa in spontaneous intracranial hemorrhage administered within 3 h of symptom onset, it was noted to have increased risk of adverse thrombotic events. There was no difference in the combined outcome between the rFVIIa treated groups compared with placebo and in fact, a statistically significant increase in arterial events was observed in the group receiving 80 mcg kg−1 rFVIIa compared with placebo.(Mayer *et al.*, 2005), (Mayer *et al.*, 2008; Mayer *et al.*, 2006). The potential for this thromboembolic complications with its use has been demonstrated in other several trials and retrospective analyses raising concern about potential harms with off label application. However, in the context of massive hemorrhage, there are potential limiting factors such as acidosis, hypothermia and refractory shock (Meng *et al.*, 2003).

The use of SOFA score for the assessment of the patient's severity of illness at the time of administration of the rFVIIa helps to predict the mortality of the patients, as it was noted to be lower in the survivor groups compared to the patient died in the hospital. Besides, it was also observed that patients with organ failure at the time of administration of rFVIIa treatment had a high mortality rate, whereas those patients without organ failure had a better prognosis (Payen *et al.*, 2016).

Problem statement & Study rationale

This study is important as there are inadequate local data regarding the usage of rFVIIa in other clinical settings especially in massive bleeding. The result obtained will help us to further evaluate the usage of rFVIIa in off label settings hence provide the basis for the development of local guidelines.

Furthermore, the effectiveness of off label usage of rFVIIa shows variable results between the studies conducted and the possible benefit of rFVIIa might be missed by usage in moribund patient and futile use in patient without massive bleeding. Proper selection of study population will provide more transparent results and avoid bias.

This study also will provide us the data of the complications that can be address to the patients and mortality rate, hence evaluate safety of off label usage of rFVIIa. Besides that, usage of blood product in the management of massive bleeding, expose patients to infections, adverse transfusion reactions and alloimmunisation. Positive role of rFVIIa in massive bleeding may avoid these complications to the patients.

Research Question(s)

Is there any comparison between the demographic data, the coagulation profile, SOFA score, thromboembolic complication and mortality rate of non-haemophilia patients treated with and without rFVIIa during massive bleeding?

What is the Sequential Organ Failure Assessment score (SOFA) of patients before receiving rFVIIa during massive bleeding?

Is there any associated factors of patients receiving rFVIIa with the overall survival?

Objective

General:

To study the treatment indications and outcomes of non-haemophilia patients treated with and without rFVIIa during massive bleeding in Hospital Universiti Sains Malaysia (HUSM)

Specific:

1. To compare the laboratory, and clinical outcome of patients treated with and without rFVIIa during massive bleeding on
    a) Coagulation profile
    b) SOFA score
    c) Thromboembolic complications
    d) Mortality rate
    e) Total blood products requirement

2. To determine the associated factors of the patients treated with rFVIIa and the overall survival.

Literature review

A study by Karkouti, 2005, titled Recombinant factor VIIa for intractable blood loss after cardiac surgery: a propensity score–matched case-control analysis, may represent the best currently available method for determining the safety and effectiveness of rF-VIIa in its patient population. He compared the outcomes of the first 51 cardiac surgery patients who were treated at the institution with rF-VIIa for intractable haemorrhage to 51 matched control patients, with propensity matching techniques to identify the control patients from a large, prospectively collected, and validated institutional database. They were able to reduce the bias in the assessment of

the treatment effects by using propensity analysis to match the treated patients to the control patients with respect to multiple confounding variables. In the results, it was noted marked reduction of INR after administration of rFVIIa. The use of blood products significantly reduced after treatment of rFVIIa. However, the incidence of adverse events was about similar between the two groups (Karkouti *et al.*, 2005).

In a retrospective case control study of recombinant factor VIIa in patients with intracranial haemorrhage caused by trauma by Emma Deloughery, a total of 35 patients who received rFVIIa were included in the study. As per Oregon Health Sciences University (OHSU) protocol, all trauma patients received a single dose of 90 lg/kg rFVIIa. The rFVIIa patients were matched with control patients using the OHSU Trauma Registry Data Base by age, gender, Glasgow Coma Scale (GCS) and Injury Severity Score (ISS). The patients were divided into two groups: those who received rFVIIa, and those who did not. It was noted that those patients who received rFVIIa had a higher rate of death (45.7% vs. 14.3% P = 0.001) compared to matched controls despite the same rate of thromboembolic complications (5.7% vs. 5.7%). In this case control study, the use of rFVIIa was not beneficial with the risk of mortality increase regardless of the severity of the injury (DeLoughery *et al.*, 2011).

One of the biggest unknowns in the off-label use of rFVIIa is the safety profile of the drug. rFVIIa is a very potent agent and ought to predispose susceptible patients to thromboembolic complications such as stroke, myocardial infarct (MI), and deep vein thrombosis. The safety should become increasingly clearer as clinical experience encourages us to use this medication earlier and in a broader spectrum of patients. In the haemophilia population, relatively few thrombotic events have been associated with the use of rFVIIa. Data in trauma patients are less clear.

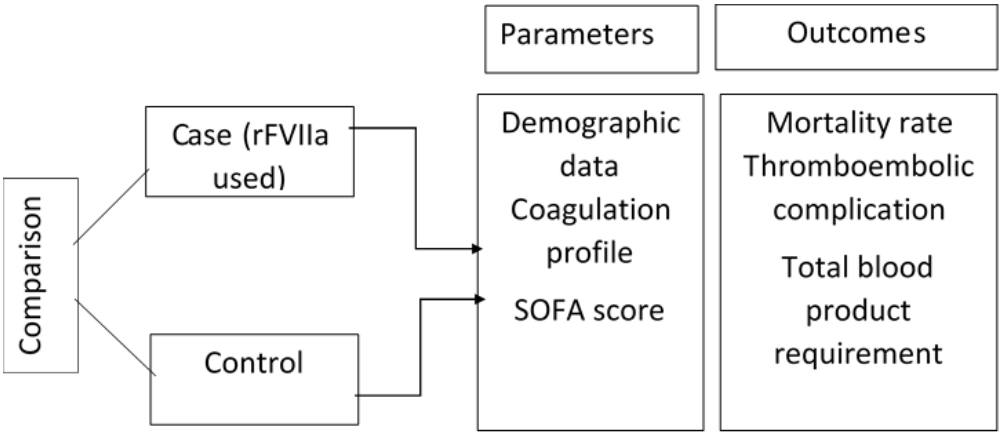
The most comprehensive appraisal of existing data is the Cochrane review conducted by Stanworth and colleagues, who evaluated 13 trials with a total of 1,938 patients. This review demonstrated mixed results. While the administration of rFVIIa was shown to reduce blood product administration (relative risk [RR] = 0.85) it was noted that the relative risk of a thromboembolic event (RR = 1.25) was elevated after rFVIIa administration. The most promising finding from this review was that rFVIIa was found to reduce coagulopathy from injuries. It was also noted that 50% of all patients treated with rFVIIa have survived to hospital discharge (Lin *et al.*, 2011).

The Sequential Organ Failure Assessment (SOFA) score is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal and neurological) graded from 0 to 4 according to the degree of failure. It is a reliable and accurate assessment of the severity of a patient's illness.

SOFA	0	1	2	3	4
Pa_{O2}/ FI_{O2}	>400	≤400	≤300	≤ 200	≤100
Platelets (10^9 /L)	>150	≤150	≤100	≤50	≤20
Hypotension	Nil	MAP <70 mmHg	Dp <5 or Db (any dose)	Dp > 5 EPI 0.1 or NOR 0.1	Db>15, EPI >0.1 or NOR >0.1
Bilirubin (umol/L)	<20	20-32	33-101	102-204	>204
GCS	15	13-14	10-12	6-9	>6
Creatinine (umol/L)	<110	110-170	171-299	300-440	>440
Urine output (ml/day)				<500	<200

Bowles and colleague stated in the study of predicting response to recombinant factor VIIa in non-haemophiliac patients with severe haemorrhage, 2006, where the records of patients treated with rFVIIa at Addenbrooke's Hospital were reviewed, the SOFA scores were significantly lower in the group that survive than the group that died. Besides that, the patient who survived have significant reduction in blood product requirement after rFVIIa (Bowles, 2006).

Conceptual framework



Research design

This is a retrospective case control study using medical record review from year 2006 to recent.

Study area

Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Kelantan

Study duration

Study will be conducted from March 2018 till March 2019. The collection of data will be taken from 2006 to recent.

Study population

The reference population will be the patients presented with massive bleeding in Kelantan. The target population will be the patients who presented with massive bleeding in HUSM. The sampling pool is the patients presenting with massive bleeding (simple random sampling) in HUSM. The sampling frame will be taken from the pharmacy registry of patients receiving rFVIIa, patients received more than 4 PC or had Massive Transfusion Protocol activated traced from blood bank record and the hospital record registry.

Subject criteria

Case	
Inclusion Criteria	**Exclusion Criteria**
Age above 18 years old Presented with massive bleeding Admission to the ward >24 hours Receive recombinant FVIIa	Patients with haemophilia or congenital bleeding disorder Patients on anticoagulant Missing data

Control	
Inclusion Criteria	**Exclusion Criteria**
Age above 18 years old Presented with massive bleeding Admission to the ward >24 hours Did not receive recombinant FVIIa	Patients with haemophilia or congenital bleeding disorder Patients on anticoagulant Missing data

Sample size estimation

The sample size required for this study are taken according to the specific objective that needed the largest sample which is Specific Objective 2.

The sample size was calculated by using computer software PS: Power and Sample Size Calculation version 3.0, 2009 (Dupont and Plummer, 1997).

The sample size estimation is based on a study by Bowles, 2006. The power of study is set at 0.8 with CI of 95% ($\alpha = 0.05$). From previous study, the standard deviation of SOFA score of patients at the time starting rFVIIa is 1.75 (SD) and the difference with the other group is 0.88 (δ). The sample size is 70 including 10% dropouts for one arm.

The total sample size will be 140 patients with 70 patients in the case arm and 70 patients in the control arm.