THE ROLE OF ACTIVATED RECOMBINANT COAGULATION FACTOR VII IN REDUCTION OF PERIOPERATIVE BLOOD LOSS IN NORMAL AND CIRRHOTIC PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY

Thesis Submitted For Partial Fulfillment of the M.D. Degree in Aanesthesia

By

Islam Ahmed Ossama Ibrahim
M.B., B.CH, M.S.C, Anaesthesiology
Faculty of medicine, Ain Shams University

Supervised by

Professor Amir Ibrahim Salah
Professor of Anaesthesia and Intensive Care
Faculty of Medicine – Ain Shams University

Professor Adel Mikhaeal Fahmy
Professor of Anaesthesia and Intensive Care
Faculty of Medicine – Ain Shams University

Doctor Hadeel Magdy Abdel Hamid
Lecturer of Anaesthesia and intensive care
Faculty of Medicine – Ain Shams University

Faculty of medicine
Ain Shams University
2011

I. Introduction

Reconstruction surgery of pelvis and acetabulum can be associated with large volume of blood loss, despite the use of intraoperative red blood cells transfusion and other blood components are still needed in most patients undergoing these complex surgical procedures (**Cryer et al., 1988).**

Blood transfusion is associated with a number of infectious and non–infectious complications. Hence, several blood conservation approaches and haemostatic agents have been investigated with the aim of reducing blood loss and the need for allogenic blood components (**Pomper et al., 2003).**

Cirrhotic patient with prolonged prothrombin time are known to have low levels of factor VII. Because the current modalities to correct this problem are not ideal, recombinant factor VII a may be useful in correcting the prolonged PT observed in the coagulopathy of cirrhosis **(Bernstein et al., 1997**).

Recombinant activated factor VIIa was originally developed to treat bleeding in hemophiliacs with anti-bodies to factor VIII and IX. At present, rFVIIa is approved in the European Union for this indication and also for the treatment of bleeding in fVII deficiency and Glanzmann thromboasthenia refractory to platelet transfusion (**Roberts et al., 2004).**

II. Aim of the work

The aim of this study is to investigate the efficacy of rFVIIa on reducing intra and postoperative blood loss in patients with normal haemostasis and cirrhotic patients undergoing total hip arthroplasty (THA).

III. Patients and Methods

After patient's written consent, 40 patients of both sexes aged 52-77 year old with fracture of femur neck in hospitals of Ain Shams University were studied during unilateral THA.
Patients were divided according to preoperative ultrasonography (U/S) findings into two groups:
20 patients who considered with normal liver (N) were of ASA I-II physical status, those patient were subdivided according to administration of the drug into two groups:

- Group (Nn) of 10 patients who received rFVIIa (novoseven).
- Group (N) of 10 patients who did not receive it.

The other 20 patients who considered with cirrhotic liver (C) and were evaluated by Child- Pugh classification are subdivided according to administration of drug into two groups:

- Group (Cn) of 10 patients who received rFVIIa (novoseven).
- Group (C) of 10 patients who did not receive it.

Exclusion Criteria

Exclusion criteria for normal patients (N) were cardiac insufficiency (NYHA class III-IV), renal insufficiency (Creatinine > 2mg %), history of thrombosis, known congenital bleeding disorder, use of non-steroidal anti-inflammatory drugs or previous receipt of rFVIIa within 48hs,known or suspected allergy to any drug that may be administrated during the course of the study.

Exclusion criteria for cirrhotic patients (C) were that of normal patients plus; overt bleeding including GIT bleeding, treatment with prothrombin concentrate, vasopressin or antifibrinolytics within 7 days, hepatocellular carcinoma or other malignancies.

- ## Technique

  Routine investigation done preoperatively included:

  - ECG
  - Chest x-ray
  - Complete blood count
  - Prothrombin time ,partial thromboplastin time and INR
  - Liver function tests and kidney function tests

Prophylactic anticoagulant with low molecular weight heparin (clexane) 20 mg. s.c. was given once a day during the preoperative period up to 12 h. before surgery and the same dose was restarted 12 h after surgery or once it was decided that no further surgical interventions was required.

After applying standard monitors (ECG, noninvasive blood pressure, ETCo2, spo2 and temperature), an intravenous cannula is placed. Ringer's solution is used to correct fluid deficit and maintenance with a dose of

4 ml/kg/h for the first 10 kg.
2 ml/kg/h for the next 10 kg.
1 ml/kg/h for each kg. above 20 kg.
None of the patients received a colloid infusion.

General anesthesia was induced using i.v fentanyl 1 ug / kg, thiopental 4-7 mg/kg and atracurium 0.5 mg/kg.

Anesthesia was maintained with 50% nitrous oxide in oxygen and Isoflurane 1%-2% from anaesthesia machine. All patients underwent endotracheal intubations. Ventilation was controlled with 8 ml/kg tidal volume and respiratory rate sufficient to maintain ETCo2 at 35-38 mm Hg.

Supplementary doses of atracurium and fentanyl were given as needed during surgery. Antagonism of neuromuscular block was performed in all patients at the end of surgery by i.v neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and the trachea of all patients was extubated before transfer to the post-anaesthesia care unit.

Patients will be divided into four groups:

- Group (N) : normal patients without use of rFVII a.
- Group (Nn) : normal patients who will receive 35 ug/kg of rFVIIa as a bolus at the first skin incision
- Group (C) : cirrhotic patient without use of rFVIIa.
- Group (Cn) : cirrhotic patients who will receive 35 ug/kg of rFVIIa as a bolus at the first skin incision.

• Assessment

➢ Clinical assessment:

- Blood pressure automatically/ 5 min.
- Heart rate
- Urine output

➢ Laboratory assessment:

Blood samples were obtained from cannula before (T0) and at end of surgery (T1).coagulation profile was examined (platelet count, prothrombin time, activated partial thromboplastin time and INR), hemoglobin concentration and hematocrit value.
Fibrinolysis was evaluated by measurement of concentration of
D- dimers and FDP.

➢ Calculation of blood loss:

The perioperative period was defined as the intraoperative period combined with the 48 hours after the first dose of rFVIIa thus, perioperative blood loss is the sum of blood volume in suction apparatus minus the fluid used for irrigation by surgical team, blood in swabs and drapes by weighing and volume in postoperative wound drains for 48 hs.

➢ Calculation of blood transfusion:

By the sum of the volume of packed RBC’s transfused.

IV. Results : Will be analyzed statistically.
V. Discussion
VI. Conclusion
VII. Summary
VIII. References
IX. Arabic summary

References

- **Bernstein E, Jeffers L, Erhardtsen E and Rajender K (1997)**: Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: A preliminary study. Gastroenterology 113:1930-1937.

- **Cryer HM, Miller FB, Evers BM, et al (1998)**: Pelvic fracture classification; correlation with hemorrhage. J Trauma 28; 973-80.

- **Pomper GJ, Wu YY and Snyder EL (2003):** Risks of transfusion-transmitted infections Curr Opin Hematol 10: 412-8.

- **Roberts HR, Monro DM and Escobar MA (2004):** Current concepts of hemostasis: implications for therapy. Anesthesiology 100:722-30.

ACKNOWLEDGMENT

First and foremost I thank **ALLAH**, the most Beneficent, and the most Merciful for the fulfillment of this work.

I would like to express my sincere gratitude to **Professor Amir Ibrahim Salah**, professor of Anaesthesia and intensive care, Faculty of Medicine, Ain Shams University, who honored me by his great support and his kind supervision.

I am, as well greatly indebted to **Professor Adel Mikhael Fahmy,** professor of Anaesthesia and intensive care, Faculty of Medicine, Ain Shams University for his encouragement and support revising this work.

I would like to express my deepest thanks to **Dr Hadeel Magdy Abdel Hamid**, lecturer of Anaesthesia and intensive care, Faculty of Medicine, Ain Shams University, who sincerely helped writing and editing this work and for her supervision.

Finally, I would like to express my gratitude for **My Parents** who took me by the hand to where I stand now, and to **My Wife** who has become a major force in my life, pushing me forward to success.

Islam A. Osaama

List of Contents

List of Figures

List of Tables

List of Abbreviations

2,3 DPG	2,3 diphosphoglycerate
ACT	Activated clotting time
ADP	Adenosine diphosphate
APTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiology
ATP	Adenosine triphosphate
BHK	Baby hamster kidney cells
BT	Bleeding time
C	Cirrhotic patients without use of rFVIIa
Cn	Cirrhotic patients with use of rFVIIa
CPD	Citrate, Phosphate and Dextrose
CT	Clotting time
DD	D-dimers
DIC	Disseminated intravascular coagulopathy
ECG	Electrocardiograph
FDP's	Fibrin degradation products
FFP	Fresh frozen plasma
HCT	Hematocrit value
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HLA	Human leucocytes antigen
IgA	Immunoglobulin A
INR	International Normalized Ratio
ITP	Idiopathic thrombocytopenic purpura
KDa	Kilo Dalton(molecular weight)
N	Normal patients without use of rFVIIa
Nn	Normal patients with use of rFVIIa
NIBP	Noninvasive blood pressure
NYHA	New York Heart Association
PC	Platelet count
PF4	Platelet factor 4
PT	Prothrombin time
RBCs	Red blood cells
rFVIIa	Recombinant activated factor VII
SCT	Sonoclot test

TEG	Thromboelastograph
TF	Tissue factor
TT	Thromboplastin time
TTP	Thrombotic Thrombocytopenic Purpura
TXA2	Thromboxane A2
WHO	World Health Organization

Introduction

Reconstruction surgery of pelvis and acetabulum can be associated with large volume of blood loss, despite the use of intraoperative red blood cells transfusion and other blood components are still needed in most patients undergoing these complex surgical procedures ***(Cryer et al., 1988)***.

Blood transfusion is associated with a number of infectious and non–infectious complications. Hence, several blood conservation approaches and haemostatic agents have been investigated with the aim of reducing blood loss and the need for allogenic blood components ***(Pomper et al., 2003)***.

Besides a variety of optional measures to compensate for blood loss, recently recombinant blood coagulation factor VIIa became available to treat patients with hemophilia with inhibitors of coagulation factors IX or X, rFVIIa has also used to treat other causes of severe bleeding; for instance, in cirrhotic patients scheduled for orthotopic liver transplantation, for thrombocytopenic patients, or for patients suffering from Glanzmann thromoasthenia ***(Salppendal et al., 2002)***.

Recombinant factor VIIa forms a complex with tissue factor (TF) that is present in the wound bed, and thereby acts as a catalyst of local blood coagulation, The

TF/rFVIIa complex activates FX to FXa, leading to the generation of thrombin (FIIa) and subsequent fibrin formation. In healthy nonhemophiliacs this thrombin generation leads to the activation of cofactors V and VIII, as well as to the accumulation of activated thrombocytes at the site of injury. This explains the excellent efficacy of rFVIIa in patients with hemophilia A or B respectively ***(Hendrik et al., 2001)***.

The coagulopathy of cirrhosis is a leading factor contributing to the high morbidity and mortality associated with liver disease in United States ***(Carr, 1989)***.

Cirrhotic patient with prolonged prothrombin time are known to have low levels of factor VII. Because the current modalities to correct this problem are not ideal, recombinant factor VII a may be useful in correcting the prolonged PT observed in the coagulopathy of cirrhosis ***(Bernstein et al., 1997)***.

Administering rFVIIa to patients with liver cirrhosis may result in additional thrombin generation and since thrombin generation is one of the most powerful existing activators of thrombocytes, the additional rFVIIa induced thrombin generation might compensate for the reduced amount of thrombocytes available and the associated decrease thrombin generation ***(Meijer et al., 2000)***.

rFVIIa appears to offer several advantages over fresh frozen plasma (FFP) and other lines of treatment in the

correction of the coagulopathy of cirrhosis. FFP is derived from pooled blood products, and the exact factor composition of each unit is highly variable. Because decreased factor VII levels appears to be the main factor contributing to the prolonged prothrombin time (PT) found in cirrhotic, it is conceivable that the low levels of factor VII in some units of FFP may not adequately correct the PT. rFVIIa is the product of recombinant technology, and therefore, the risk for the transmission of blood-borne disease present with the use of FFP is nonexistent with rFVIIa. Besides; the duration of effect of a unit of FFP is 3-4 hours, whereas the duration of effect or rFVIIa is dose dependant, with the shortest mean effect being 120 minutes in the lowest dose range and 720 minutes in the highest dose range ***(Lusher, 1996)***.

rFVIIa should not be regarded as the universal solution for disorders of coagulation; there are limitations to its rational use. Each dose of the protein is currently exceedingly expensive. The clearance of rFVIIa is approximately 30-35 ml/kg/h in adults and greater in childrens requiring repeated dosing approximately every 2 hours for maintenance of efficacy ***(Kenet et al., 1999)***.