Effect of Recombinant Activated Factor VII (rFVIIa) on Intraoperative Blood Loss during Pediatric Brain Surgery [A Clinical and Thromboelastographic Study]

Thesis

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ABSTRACT

There is a clinical need for one or more new hemostatic agents to supplement a help in controlling bleeding in pediatric brain tumor, which cannot be controlled by surgical intervention, local hemostatic agents and transfusion of blood products.

Recombinant activated factor VII has been approved by the U.S Food and Drug Administration (FDA) for nearly a decade for the prevention and treatment of bleeding episodes in hemophilic patients with inhibitors to coagulation factor VIII or factor IX. An increasing number of case series and reports have described its efficacy in preventing and controlling massive hemorrhage in pediatric brain surgery.

In this study, both prophylactic and therapeutic effects of rFVIIa. were investigated, with different two doses; low dose (30 $\mu g.Kg^{-1}$) and moderate dose (60 $\mu g.Kg^{-1}$).

45 patients were randomly allocated into 3 groups, control group, 30 $\mu g.Kg^{-1}$ group, 60 $\mu g.Kg$ $group^{-1}$.

It was concluded that administration of recombinant factor VIIa resulted in a dose-dependent reduction of intraoperative blood-loss compared with control group.

Regarding the prophylactic effect of rFVIIa in a dose of 30 $\mu g.Kg^{-1}$ is not effective as in a dose of 60 $\mu g.Kg^{-1}$, as only 4 patients in rFVIIa 30 μg group (26.67%) didn't need a second therapeutic dose, while 8 patients in rFVIIa 60 μg group (53.33%) didn't need a second therapeutic dose which considered a very good result that more than the half of the patients of this group treated only with a single prophylactic dose.

Regarding the therapeutic effect, we can say that the dose of 60$\mu g.Kg^{-1}$ is slightly more effective than 30 $\mu g.Kg^{-1}$dose.

Keywords:

rFVIIa, Hemostasis, coagulopathy, Bleeding, Uncontrolled, neurosurgery (brain surgery), pediatric.

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ABBREVIATION

α: Alpha angle

ABGs: arterial blood gases

ADH: Antidiuretic hormone

ALT: Alanine transaminase

ANH: Acute normovolemic hemodilution

APAP: acetaminophen overdose

APTT: Activated partial thromboplastin time

ASA: American Society of Anesthesia

AST: Aspartate transaminase

AT: Antithrombin

ATIII: Antithrombin III

CBC: complete blood count

CT: coagulation time

CFT: clot formation time

CL: clearance

CVP: central venous pressure

DIC: Disseminated intravascular coagulopathy

DO2: Oxygen delivery

DVT: deep venous thrombosis

EBV: Estimated blood volume

ECF: Extracellular fluid

ECG: Electrocardiogram

ECMO: Extra corporeal membrane oxygenator

FDA: Food and Drug Administration

FFP: Fresh frozen plasma

g: gram

GBMs: glioblastoma multiform

GI: Gastrointestinal

h: Hour

Hb: Hemoglobin

HBV: Hepatitis B virus

Hct: Hematocrit

HCV: Hepatitis C virus

HES: Hydroxyethylstarch

HIV: Human immunodeficiency virus

HL: Lowest acceptable Hct

ICF: Intracellular fluid

ICH: Intracranial hemorrhage

ICR: Interquartile range

INR: International normalized ratio

IV: Intravenous

Kg: Kilogram

L: Liter

LOS: length of stay

MA: maximum amplitude

MABL: Maximal allowable blood loss

mg: milligram

Min: Minute

mL: milliliter

MOF: Multiorgan system failure

n: number

O2ER: Oxygen extraction ratio

OLT: Orthotopic liver transplantation

PABD: Preoperative autologous blood donation

Plt: Platelets count

PC: Prothrombin concentration

PCCs: Prothrombin complex concentrates

PT: Prothrombin time

p*v*O_2: Mixed venous partial pressure of oxygen

Q: cardiac output

RBCs: Red blood cells

RCTs: Randomized controlled trials

rFVIIa: RecombinantActivated factor VII

RT: Reaction time

RhD: Rhesus D antigen

SaO_2: Arterial O_2 saturation

SvO_2: Mixed venous O_2 saturation

TEG: Thromboelastography

***t*1/2:** Half life

TBI: Traumatic brain injury

TF: Tissue factor

TFPI: Tissue factor pathway inhibitor

TM: Thrombomodulin

TPA: Tissue plasminogen activator

VO_2: Oxygen uptake

U: Unite

***V*ss:** Volume of distribution at steady state

vWF: Willebrand factor

WB: whole blood

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INTRODUCTION

Hemorrhage is a recognized complication of neurosurgical procedures on the brain [(1)]. Brain tumors are the most common tumors of childhood [(2,3)]. Tumor resection is a standard treatment option, but it may be complicated with significant blood loss due to tumor pathology, location, and/or vascularity. Unfortunately, hemostatic sponges and infused hemostatic factors derived from blood products are sometimes ineffective in stopping blood loss. On some occasions clamping of cerebral blood vessels, partial brain tissue resection or reoperation is necessary to achieve hemostasis. Such procedures can result in disturbance or loss of brain function, with subsequent patient disability and/or other neurological sequelae [(1)].

Massive hemorrhage after complicated surgical procedures is frequently a combination of surgical and coagulopathic bleeding. Surgical bleeding originates from a recognizable source at the site of surgery or trauma and is typically corrected using surgical measures, such as packing, or tamponading the bleeding area, ligating the damaged vessels, or inducing localized thrombosis via invasive radiology [(4)]. Coagulopathic bleeding results from impaired thrombin generation.

The conventional treatment of coagulopathic bleeding involves administration of blood products, such as RBCs, fresh frozen plasma, cryoprecipitate and platelets to replace the blood components lost in the process of diffuse hemorrhage. However, such replacement therapy is associated with increased risks of mortality and morbidity. These include complications such as ABO incompatibility, transfusion-related acute lung

injury, multi-organ dysfunction syndrome and transmission of infectious agents [5].

The advent of a new, potentially very potent, hemostatic agent, recombinant activated blood coagulation Factor VII, is welcomed in the neurosurgical setting [1].

Recombinant activated factor VII (rFVlIa) is a hemostatic agent developed for treatment of bleeding episodes in hemophilia patients with high titer inhibitors [6]. It was approved for use in Europe in 1996 and Food and Drug Administration (FDA)-approved in 1999 for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors. rFVlIa was subsequently used for patients with life-threatening hemorrhage associated with massive trauma, surgery, thrombasthenia (e.g. Glanzmann's), congenital factor VII deficiency, acquired factor VIII or IX inhibitors, liver failure and other medical situations in which life-threatening hemorrhage was not responsive to conventional therapeutic interventions [7].

Recombinant FVIIa has been used recently in the treatment of massive bleeding in nonhemophilic patients during surgery [1]. It can be used to reduce blood loss and transfusion requirements in elective surgical procedures associated with excessive bleeding.

The effect of rFVIIa can be assessed by laboratory investigations [e.g. hemoglobin (Hb), hematocrit (Hct), platelets count (Plt), activated partial thromboplastin time (aPPT), prothrombin time (PT), prothrombin concentration (PC), international normalized ratio (INR), and fibrinogen level] and thromboelastography.

Thromboelastography (TEG) is a viscoelastic measure of the whole blood coagulation and fibrinolysis that has influenced perioperative coagulation monitoring and therapy during cardiopulmonary bypass [(8)], orthotopic liver transplant [(9)], and in patients with qualitative platelet dysfunction. TEG is a very sensitive tool in detecting coagulation defects that can not be detected by routine laboratory tests [(10)]. Whole blood elasticity as measured by TEG has been shown to improve following rFVIIa therapy. In-vivo and ex-vivo TEG measurements show that rFVIIa shortens whole blood clotting time [(11)]. TEG monitoring provide continuous assessment of clot firmness to measure the onset of coagulation time (CT) [standard TEG: reaction time (r), the kinetics of clot formation [clot formation time (CFT)] [standard TEG: coagulation time (K)] and maximal amplitude (MA) [(11)].

Hypothesis:

It is hypothesized that rFVIIa use in pediatric brain surgery may be effective in reducing blood loss and transfusion requirements of different blood products e.g. packed RBCs, platelets and fresh frozen plasma.

Aim of the work:

The study is targeting at the evaluation of the efficacy of rFVIIa in reducing blood loss during pediatric brain surgery. It is a clinical and thromboelastographic study.

Chapter 1

PHYSIOLOGY OF HEMOSTASIS

Hemostasis:

The ability of the body to control the flow of blood following vascular injury is necessary to continued survival. The process of blood clotting and then the subsequent dissolution of the clot, following repair of the injured tissue, is termed hemostasis [(12)].

Normally, endothelium is protected from spontaneous thrombus formation by the constitutive expression of native anticoagulants such as heparin. Heparin's anticoagulant effect comes from its ability to increase the activity of antithrombin (AT) and thrombomodulin (TM). Endothelium also releases nitric oxide, prostacyclin, and tissue plasminogen activator (TPA) intravascularly to enhance blood flow. Physical (surgery or trauma), chemical, or cellular damage to the vascular lining activates the local endothelium. Once activated, these anticoagulant molecules are removed and downregulated, whereas procoagulants molecules are expressed and upregulated [(12)].

Pathways of Hemostasis:

Early models of coagulation:

In 1960, hemostasis was viewed as a sequential series of steps in which activation of one clotting factor led to the activation of another, finally leading to a burst of thrombin generation. Each clotting factor was thought to exist as a proenzyme that could be converted to an active enzyme [(13)].

The original cascade models were subsequently modified to include the observation that some procoagulants were cofactors and did not possess enzymatic activity. In addition, the clotting sequences were divided into so-called extrinsic and intrinsic systems, as shown in **Fig. (1)**[(12)].The extrinsic system consisted of factor VIIa and tissue factor (TF), the latter being viewed as extrinsic to the circulating blood. The factors in the so-called intrinsic system were all viewed as being intravascular. Both pathways could activate factor X, which, in complex with its cofactor Va, could convert prothrombin to thrombin. While these earlier concepts of coagulation were extremely valuable, several groups recognized that the intrinsic and extrinsic systems could not operate independently of one another and that all the clotting factors were somehow interrelated. Only in this way could hemostasis in vivo be explained [(12)].

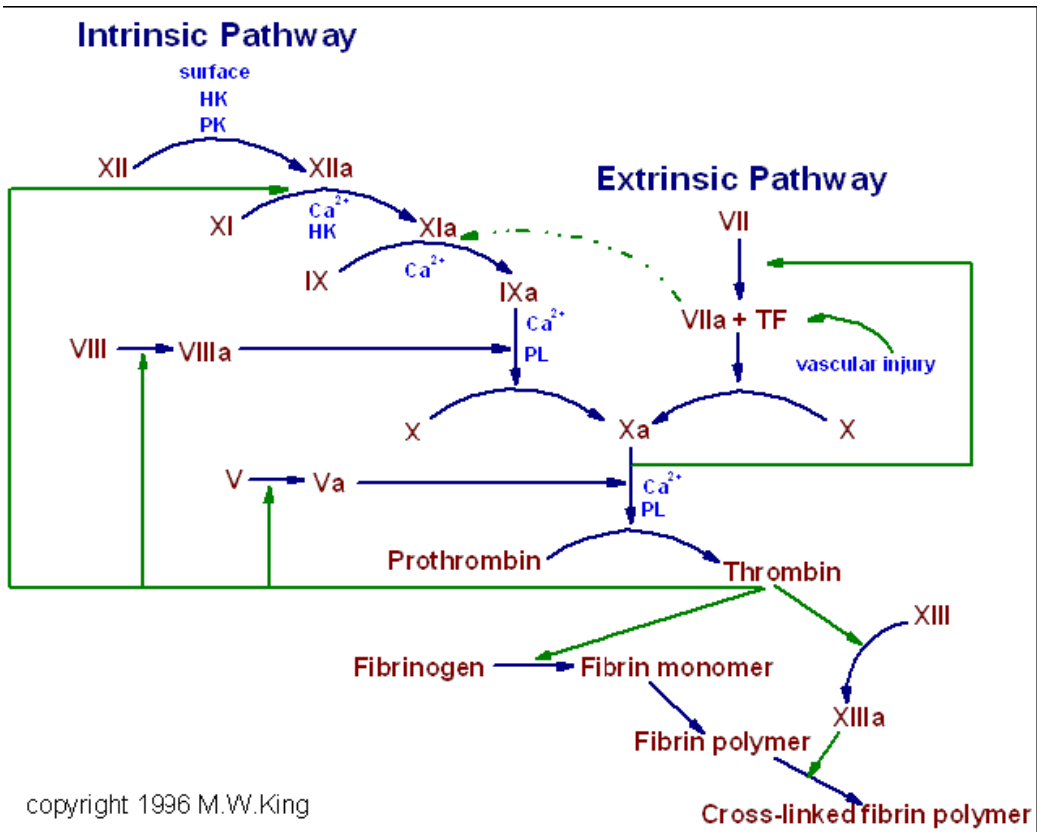

Fig. (1): The clotting cascades[(12)].