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Effect of Unfractionated Heparin in Treatment of Sepsis

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List of Abbreviations

ACCP/ SCCM	= American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee.
ACTH	= Adrenocorticotrophic hormone
ALT	= Alanine transaminase
APACHEII	= Acute Physiology and Chronic Health Evaluation II
APC	= Activated protein C
APCs	= Antigen presenting cells
aPTT	= activated Partial Thromboplastin Time
ARDS	= Acute respiratory distress syndrome
AST	= Aspartat transaminase
AT	= Antithrombin
AT-III	= Antithrombin -III
Anti-Xa HA	= Antifactor Xa heparin assay
BP	= Blood pressure
CD4	= Cluster of differentiation 4
CRP	= C reactive protein
CRRT	= Continuous renal replacement therapy
DIC	= Disseminated Intravascular Coagulopathy
DVT	= Deep Venous Thrombosis
EGDT	= Early goal directed therapy
FM	= Fibrin monomers

GP	=Glycoprotein
HIT	= Heparin Induced Thrombocytopenia
HLA	= Human leukocyte antigen
HMGB1	= High-mobility group B-1 protein
HVHF	= High volume haemofiltration
INR	=International Normalized Ratio
I.V.	= Intravenous
ICU	= Intensive Care Units
IL	= Interleukin
KDa	= kilo Dalton
LDH	=Lactate dehydrogenase
LMWH	= Low Molecular Weight Heparin
LOS	= Length of stay
LPS	= Lipopolysaccharide
MHC	=Major Histocompatibility complex
MODS	=Multiple Organ Dysfunction Syndrome.
MRSA	= Methicillin-resistant Staphylococcus aureus
MSSA	= Methicillin-sensitive Staphylococcus aureus
NK cells	=Natural Killer cells
NO	=Nitric Oxide
PAI-1	= Plasminogen activator inhibitor type-1
PCT	=Procalcitonin
PF4	=Platelet factor 4
Plg	=Plasminogen
PS	= protein S

PT	=Prothrombin time
S.C	=Subcutaneous
SIRS	=Systemic inflammatory response syndrome
TAT	= Thrombin-antithrombin complex
TF	=Tissue factor
TFPI	=Tissue factor pathway inhibitor
Th1	=Type 1 helper T-cell
Th2	=Type 2 helper T-cell
TM	= Thrombomodulin
TNF	= Tumor necrosis factor
TP	=Terlipressin
t-PA	= tissue-type plasminogen activator
UFH	= Unfractionated heparin

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Introduction

Sepsis is considered a leading cause of death worldwide in non cardiogenic intensive care units with approximately 18 million cases annually and a mortality rate of almost 30%. Mortality of severe form is still elevated in spite of the progress in the antibiotic therapy and in haemodynamics and respiratory support (*Baudo and de Cataldo, 2000*).

The most frequent cause of death is the Multiple Organ Dysfunction Syndrome (MODS). The excessive inflammatory reaction and the damage of the microvascular bed secondary to the inflammation and to the disseminated intravascular coagulopathy (DIC) are important pathogenic factors (*Dhainaut et al, 2005*).

The activation of coagulation cascade is an early and common response to the infectious challenge. In turn, most of the molecules involved in the procoagulant state that characterizes sepsis (e.g., thrombin) are also powerful generators or amplifiers of the inflammatory response (*Collins et al, 2006*).

In sepsis a complex system of cellular activation initiates the release and the interaction of activators and inhibitors of the

inflammation (cytokines), the activation of the enzymatic cascade systems (coagulation, fibrinolytic and complement systems) and the synthesis of proteases and anti proteases. The activation of the coagulation system, uncontrolled by the fibrinolytic system with formation of fibrin in the microvascular bed, has an important role in MODS (*Jaimes and de la Rosa, 2006*).

The rationale behind anticoagulant treatments is that certain factors [e.g.; activated protein C (APC), antithrombin (AT), and tissue factor pathway inhibitor (TFPI)] are depleted and the use of recombinant technology or plasma-purified derivatives may replenish them (*Opal et al, 2002*).

In contrast, heparin (a naturally occurring proteoglycan) does not simply replenish what sepsis patients have depleted. As a consequence of activation of coagulation cascade, heparin dramatically reduces thrombin generation and fibrin formation (*Jaimes and de la Rosa, 2006*).

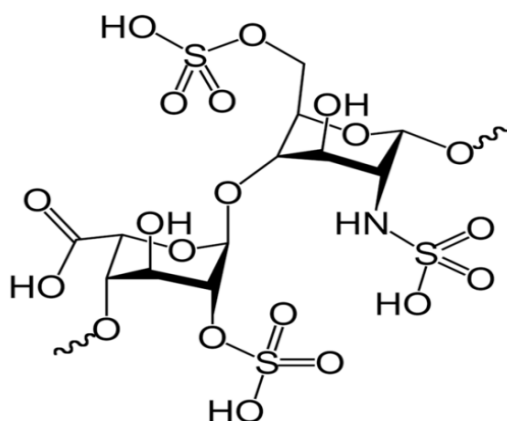
Animal and human models have suggested that heparin, in addition to successfully inhibiting the coagulation cascade in sepsis, may also modulate a wide array of response to infection (*Tanaka et al, 1990*).

Aim of the Work

To evaluate the effect of addition of low dose of unfractionated heparin to the standard treatment strategy for septic patients on hospital stay and 28-day all-cause mortality.

What is heparin?

Native heparin is a polymer with a molecular weight ranging from 3 kilo-Dalton (kDa) to 30 kDa, although the average molecular weight of most commercial heparin preparations is in the range of 12 kDa to 15 kDa. Heparin is a negatively charged, sulphated glycosaminoglycan which is a member of the glycosaminoglycan family of carbohydrates and consists of a variably-sulfated repeating disaccharide unit (*Nader, 1999*).



(Figure 1) heparin structure (*Nader, 1999*).

The most common disaccharide unit is composed of a 2-O-sulfated iduronic acid and 6-O-sulfated, N-sulfated glucosamine, IdoA (2S)-GlcNS (6S). For example, this makes up 85% of heparins from beef lung and about 75% of those

from porcine intestinal mucosa. The rare disaccharides containing a 3-O-sulfated glucosamine (GlcNS (3S, 6S) or a free amine group (GlcNH₃⁺). Under physiological conditions, the ester and amide sulfate groups are deprotonated and attract positively-charged counter ions to form a heparin salt. It is in this form that heparin is usually administered as an anticoagulant (*Francis and Kaplan, 2006*).

Historical Highlights

Heparin was discovered by McLean in 1916, and Brinkhous and associates demonstrated that its anticoagulant effect requires a plasma cofactor later named antithrombin-III (AT-III), but is now known simply as AT (*Brinkhous et al, 1939*).

Rosenberg and Lam, Rosenberg and Bauer, and Lindahl elucidated the mechanisms responsible for the heparin/AT interaction. It is now known that the active center serine of thrombin and other coagulation enzymes are inhibited by an arginine-reactive site on the AT molecule and that heparin binds to lysine site on AT, producing a conformational change at the arginine-reactive site that converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor of thrombin and factor Xa (*Rosenberg and Bauer, 1994*).