جامعة عين شمس
كليــة الطــب
قسم التخدير و الرعـاية المركـزة

# تأثير عقار الهيبارين الغير مجزأ في علاج مرض تعفن الدم

*رساله مقدمه توطئة للحصول على درجة الدكتوراه فى التخدير مقدمة من:*

**الطبيبة / سندس أحمد إبراهيم**
بكالوريوس الطب والجراحه. ماجستيرالتخدير
كلية الطب.جامعة عين شمس

*تحت إشراف*

**استاذ دكتور/ بهاء الدين عويس حسن**
استاذ التخدير والرعاية المركزة
كلية الطب. جامعة عين شمس.

**استاذ دكتور/ شريف وديع ناشد**
استاذ التخدير والرعاية المركزة
كلية الطب. جامعة عين شمس.

**دكتور/ هديل مجدي عبد الحميد**
مدرس التخدير والرعاية المركزة
كلية الطب. جامعة عين شمس .

**دكتور/ مايار حسن السرسي**
مدرس التخدير والرعاية المركزة
كلية الطب. جامعة عين شمس.

**كلية الطب**

**جامعة عين شمس**

**(٢٠١٢)**

*Ain Shams University*
*Faculty of Medicine*
*Department of Anesthesia and Critical Care*

# Effect of Unfractioned Heparin in Treatment of Sepsis

*Thesis Submitted for Partial Fulfillment of M.D. Degree in Anesthesia*
*Presented by:*

**Sondos Ahmad Ibrahim**
*M.B.B.Ch., M.Sc. of Anaesthesia*
*Faculty of medicine, Ain Shams University*

*Supervised By*

**Prof. Dr. Bahaa Eldin Ewees Hasan**
*Professor of Anesthesiology and Intensive Care*
*Faculty of Medicine, Ain Shams University*

**Prof. Dr. Sherif Wadie Nashed**
*Professor of Anesthesiology and Intensive Care*
*Faculty of Medicine, Ain Shams University*

**Dr. Hadil Magdi Abd-El Hamid**
*Lecturer of Anesthesiology and Intensive Care*
*Faculty of Medicine, Ain Shams University*

**Dr. Mayar Hasan El sersi**
*Lecturer of Anesthesiology and Intensive Care*
*Faculty of Medicine, Ain Shams University*

**Faculty of medicine**
**Ain Shams University**
**(2012)**

# Acknowledgments

*First of all, all gratitude is to* **ALLAH** *for blessing this work until it has reached its end, as a part of his generous help throughout my life.*

*I would like to express my deepest gratitude to* ***Prof. Dr. Bahaa Eldin Ewees Hasan,*** *Professor of Anesthesia and Critical Care, Faculty of Medicine - Ain Shams University, for the great support and encouragement he gave me throughout the whole work. It is an honor to work under his guidance and supervision.*

*I also wish to thank* ***Prof. Dr. Sherif Wadie Nashed*** *professor of Anesthesia and Critical care, Faculty of Medicine - Ain Shams University, for his kind guidance and revision for the whole work.*

*This work would have never been completed without the great help, close supervision offered by* ***Dr. HADEEL Magdi*** *lecturer of Anesthesia and Critical Care, Faculty of Medicine - Ain Shams University.*

*I am deeply indebted to* ***Dr. Mayar Hassan El-Sersi*** *lecturer of Anesthesia and Critical Care, Faculty of Medicine - Ain Shams University, for her close observation and faithful advices.*

**Sondos Ahmad**

Table of Contents *Page*

# 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** = Continous 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** | = Unfractioned heparin |

# List of Figures

# List of Tables

# 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 haemodyamics 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).*

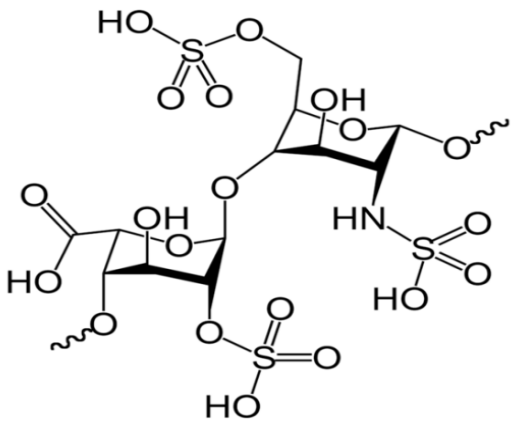
Animal and human models have suggested that heparin, in addition to successfully inhibiting the coagulation cascade in sepsis, may also modulate a wide array of response to infection *(Tanaka et al, 1990).*

# Aim of the Work

To evaluate the effect of addition of low dose of unfractioned 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 ($GlcNH_3^+$). 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).*