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A comparison between continuous intravenous infusion versus intermittent bolus doses of Hydrocortisone for circulatory support in patients with sepsis

Thesis submitted for partial fulfillment of M.D. degree in anesthesia
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Ain Shams University

Faculty of Medicine 2015

DIDICATION

To my parents, wife, Son (Mustafa) for their continuous support and encouragement

Acknowledgment

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 El Din Ewaiss*** *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. I had the privilege to benefit from his great knowledge, and it is an honor to work under his guidance and supervision.*

Prof. Basel Nour El Din *Professor of Anesthesia and Critical Care, Faculty of Medicine - Ain Shams University is such a kind, respectable and supportive mentor, it is really a great honor to work under your supervision.*

I also wish to thank ***Ahmed Nagah El Shaer ,*** *Professor of Anesthesia and Critical care, Faculty of Medicine - Ain Shams University, for his great help in every step in the work and for his kind guidance and meticulous revision for the whole work.*

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

Amr Mohamed Hilal

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ABBREVIATIONS LIST

ABG : Arterial blood gases

ABP : Arterial blood pressure

ADH : Antidiuretic hormone

ALI : Acute lung injury

ANP : Atrial natriuretic peptide

APACHE : Acute physiology and chronic health evaluation

APC : Activated protein C

APS : Acute physiology score

aPTT : Activated partial thromboplastin time

ARDS : Acute respiratory distress syndrome

ARF : Acute renal failure

ATP : Adenosine triphosphate

AVP : Arginine vasopressin

BP : Blood pressure

bpm : beat per minute

BSI : blood stream infection

BUN : Blood urea nitrogen

CaO_2 : Arterial oxygen content

CHF : Congestive heart failure

CI : Cardiac index

CNS : Central nervous system

CO : Cardiac output

Cr.Cl. : Creatinine clearance

CRP : C-reactive protein

$C\tilde{v}O_2$: Mixed venous oxygen content

CVP : Central venous pressure

CVS : Cardiovascular system

DBP : Diastolic blood pressure

DIC : Disseminated intravascular coagulopathy

DVT : Deep venous thrombosis

ED : Emergency department

EF : Ejection fraction

EGDT : Early goal directed therapy

FiO_2 : Fraction of inspired oxygen

GCS : Glasgow coma scale

GFR : Glomerular filtration rate

GIT : Gastrointestinal tract

Hb : Hemoglobin

HF : Heart failure

HR : Heart rate

ICU : Intensive care unit

IL : Interleukin

INR : International normalized ratio

IPP : Inspiratory plateau pressure

IQR : Interquartile Ratio

IV : Intravenous

LPS : Lipopolysaccharide

LV : Left ventricle

MAP : Mean arterial blood pressure.

Mc : Maximal Tubular Absorption Capacity

MODS : Multiorgan dysfunction syndrome

MOF : Multiorgan failure

MRSA : Methicillin-resistant Staphylococcus aureus

NAC : N-acetylcysteine

NE : Norepinephrine

NO : Nitric oxide

PA : Pulmonary artery

PAC : Pulmonary artery catheter

PAF : Platelet Activating Factor

PAO_2 : Partial pressure of alveolar oxygen tension

PaO_2 : Partial pressure of arterial oxygen tension

PAOP : Pulmonary artery occlusion pressure

PAP : Pulmonary artery pressure

PCO_2 : Partial pressure of carbon dioxide

PCT : Procalcitonin

PCWP : Pulmonary capillary wedge pressure.

PO_2 : Partial pressure of oxygen

PP : Pulse pressure

PT : Prothrombin time

PVR : Pulmonary vascular resistance

RAP : Right atrial pressure

rh APC : Recombinant human Activated protein C

RRT : Renal replacement therapy

RV : Right ventricle

S.Cr. : Serum creatinine

SAPS : Simplified Acute Physiology Score

SaO_2 : Oxygen saturation of arterial blood

SBP : Systolic blood pressure

$ScvO_2$: Central venous oxygen saturation

SD : Standard deviation

SIRS : Systemic inflammatory response syndrome

SOFA : Sequential organ failure assessment

SV : Stroke volume

SVI : Stroke volume index

$S\tilde{v}O_2$: Mixed venous oxygen saturation

SVR : Systemic vascular resistance

TFPI : Tissue factor pathway inhibitor

Th cells : Type helper cell

TLR : Toll –like receptors

TNF : Tumor necrosis factor

TPR : Total peripheral resistance

UOP : Urine output

VO_2 : Oxygen consumption

VP : Vasopressin

VR : Venous return

VRE : Vancomycin-resistant enterococcus

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INTRODUCTION

Sepsis is an infection-induced syndrome defined as the presence of two or more of the following features of systemic inflammation: hyperthermia or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or supranormal minute ventilation **(Wheeler et al., 1999).**

Sepsis, or sepsis syndrome, and septic shock are commonly used terms. Although these terms frequently predicted the development of end organ dysfunction or death, unfortunately they were frequently employed interchangeably, with consequent confusion between those with signs and symptoms of infection plus a positive culture and those without a positive culture. Even more confusion emerged when some authors considered hypotension or end organ dysfunction as parts of the sepsis syndrome, whereas others included those only in the septic shock definitions. In a Consensus Conference, a uniform set of definitions for sepsis and related syndromes was proposed and recently reviewed **(Bone et al., 1992)**

The inflammatory response occurring during sepsis is associated with diffuse impairment of endothelial structures, with consequent increase in vascular permeability. As the interface between the circulating blood and vascular smooth-

muscle cells, endothelial cells have several key functions: they actively regulate vascular tone and permeability, leukocyte extravasation, the balance between coagulation and fibrinolysis, and the proliferation of vascular smooth-muscle and renal mesangial cells **(Riedemann et al., 2003).**

Early goal-directed therapy is an algorithmic approach to hemodynamic optimization and resolution of global tissue hypoxia within the first 6 hours of disease presentation. The strategy targets normal oxygen delivery by optimizing preload, afterload, oxygen content, and contractility to achieve a balance between tissue oxygen delivery and consumption (guided by central venous pressure, mean arterial pressure, and Central venous oxygen saturation (ScvO2) monitoring **(Osborn et al., 2005).**

The use of corticosteroids as an adjunctive therapy has been controversial for decades **(Russell, 2006)**. Short course of high dose corticosteroids has been accepted therapy. Subsequent studies, however, did not confirm a survival benefit with this regimen and suggested an increase in super infection-related mortality **(Lefering et al., 1995)**. Studies that have used lower doses of hydrocortisone (200 to 300 mg per day) for longer durations have reported earlier reversal of shock and improved survival **(Annane, 2005).**

Recently, a new concept emerged using low dose long-term corticosteroids for sepsis-induced adrenal insufficiency and catecholamine-dependent sepsis. Results of small, randomized clinical trials are promising, suggesting a new role for corticosteroids in sepsis However, many observations argue that suboptimal cortisol production may be common and associated with worse outcomes. **(Bellissant et al, 2009)**.

AIM OF THE WORK

This study aims to compare the effect of continuous intra-venous infusion of low dose versus intermittent injection of bolus doses of hydrocortisone on supporting the circulation in septic patients with favorable effect on the immune response, with a trial to evaluate the value of free cortisol level as a prognostic marker of severity in patients with severe sepsis.