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Evaluation of the Safety and Efficacy of Erythropoietin in Septic Patients

Thesis Submitted for the Partial Fulfillment of

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وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
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Islam Taher

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
AIDS	Acquired immune deficiency syndrome
ARDS	Acute respiratory distress syndrome
ANOVA	A one-way analysis of variance
BBB	Blood brain barrier
Bcl-2	B-cell lymphoma 2, apoptosis regulator
CA1	Cornu Ammonis 1
CBC	Complete blood count
COPD	Chronic obstructive pulmonary disease
CLP	Cecal Ligation and Puncture
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CVS	Cerebral vascular stroke
CVP	Central venous pressure
DBP	Diastolic blood pressure
DIC	Disseminated intravascular coagulation.
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EPO	Erythropoietin
EPOR	Erythropoietin receptor
FiO_2	Fraction of inspired oxygen
g/dl	Gram per deciliter
HPV	Hypoxic pulmonary vasoconstriction
HR	Heart rate
Hr	Hour
HTN	Hypertension
ICU	Intensive care unit
IL	Interleukin
ISHD	Ischemic heart disease
IU	International unit

Jak-2	Janus tyrosine kinase 2
MAP	Mean arterial pressure
mg/dl	Milligram per deciliter
mm^3	Cubic millimeter
ml/kg	Milliliter per kilogram
mmHg	Millimeter mercury
mmol/L	Millimole per liter
mRNA	Messenger ribonucleic acid
mU/ml	Milli units/ milliliter
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
pH	Power of hydrogen
PT	Prothrombin time
PTT	Partial thromboplastin time
qSOFA	Quick sequential organ failure assessment score
RBS	Random blood sugar
rhEPO	Recombinant human erythropoietin
SaO_2	Arterial oxygen saturation
SBP	Systolic blood pressure
$ScVO_2$	Central venous oxygen saturation
SD	Standard deviation
Sec	Second
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment score
SPSS	Statistical Program for Social Science
SvO_2	Mixed venous oxygen saturation
TNF	Tumor necrosis factor
µmol/L	Micromole per liter
UOP	Urinary output
X^2	Chi-square

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INTRODUCTION:

Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management. Over the last decade there has been a demonstrable significant reduction in the mortality from severe sepsis and septic shock through the use of performance metrics and collaborative quality improvement efforts that facilitate the incorporation of the latest scientific and clinical advancement into bedside practice. ***(Levinson et al, 2011)***

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Sepsis-induced hypotension is defined as a systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 70 mmHg or a SBP decrease >40 mmHg. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. ***(Dellinger et al, 2012)***

During infection, offending microbes interact with the host immune system producing a downstream inflammatory cascade involving cytokines and other mediators, which in turn triggers a systemic response. The resultant effects include vasodilatation, increased vascular permeability, myocardial depression, and

impairment of the coagulation cascade, resulting in global imbalance of systemic oxygen supply and demand. During the late stage of sepsis, immunosuppression predominates, leading to multi-organ dysfunction and further clinical deterioration. ***(Keegan et al, 2014)***

Erythropoietin acts as the primary regulator of erythropoiesis and is used clinically to treat anemia resulting from chronic kidney disease or chemotherapy. Erythropoietin has a number of effects outside of the hematopoietic system. Erythropoietin receptors have been identified in a variety of cells including neurons, endothelial cells, cardiocytes, muscle and hair follicles, and erythropoietin has been demonstrated to play a role in protecting and potentially reversing pathologic changes in response to stressors such as ischemia/reperfusion, hypoxia, or metabolic injury. ***(Amy & Carig, 2009)***

Erythropoietin also carries anti-apoptotic and immune modulatory activities. In theory, these tissue protective properties could make erythropoietin an attractive agent for modulating the host response in sepsis. ***(Manfred et al, 2011)***

AIM OF THE WORK:

The aim of this work is to evaluate the potential benefits and risks of the use of recombinant human erythropoietin in septic patients.

SEPSIS

Sepsis which is derived from the Greek verb *sepo* (meaning —I rot) is a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection. It is a major public health concern as it is considered as a leading cause of mortality and critical illness worldwide. ***(Torio & Andrews, 2013)***

At present, there have been epidemiology studies in most developed and in many developing countries. In general, sepsis occurs in approximately 2% of all hospitalizations in developed countries. Sepsis may occur in between 6 and 30% of all intensive care unit (ICU) patients, with substantial variation due to the heterogeneity between ICUs. ***(Vincent et al, 2006)***

Estimates suggest sepsis affects millions of people a year. Sepsis is more common among males than females. The condition has been described at least since the time of Hippocrates. The terms septicemia and blood poisoning referred to the microorganisms or their toxins in the blood and are no longer commonly used. ***(Angus & Van der Poll, 2013)***

Several medical conditions increase a person's susceptibility to infection and developing sepsis. Common sepsis risk factors include age (especially the very young and old); conditions that weaken the immune system such as cancer,

diabetes, or the absence of a spleen; and major trauma and burns. ***(Rubin & Schaffner, 2014)*** (Table 1)

Disease severity partly determines the outcome with the risk of death from sepsis being as high as 30%, severe sepsis as high as 50%, and septic shock as high as 80%. ***(Jawad et al, 2012)***

Table (1): Risk factors for sepsis:

Advanced age.
Compromised immune status.
Acquired immunodeficiency syndrome.
Increased use of cytotoxic and immunosuppressant agents.
Alcoholism.
Malignancy.
Increased number of transplant recipients and transplantation procedures.
Chronic illness.
Diabetes mellitus.
Chronic renal failure.
Hepatitis.
Surgical/invasive procedures.
Malnutrition.
Broad-spectrum antibiotic use.
Increased number of drug-resistant microorganisms.

(Hotchkiss & Karl, 2003)

Definitions:

Infection:

It is defined as a pathological process caused by the invasion of a normally sterile tissue or fluid or body cavity by

pathogenic or potentially pathogenic micro-organisms. It is also important to point out that, frequently, infection is strongly suspected without being microbiologically confirmed. ***(Dellinger et al, 2013)***

Systemic inflammatory response syndrome (SIRS):

It is an inflammatory reaction that produces at least two of the following four signs:

- Abnormal body temperature: hypothermia, < 96.8°F/ 36°C; or fever, > 100.4°F/ 38.3°C.
- Tachycardia (> 90 beats/minute).
- Tachypnea (> 20 breaths/minute or a rate sufficient to produce PaCO2 < 32 mm Hg).
- Abnormal white blood cell count (> 12,000/mm3, <4000/mm3, or > 10% immature forms). ***(Gaieski & Goyal, 2013)***

SIRS due to abnormal white blood cell count can be triggered by an infection, but also it can arise from non-infectious sources such as trauma, hemorrhage, burns, surgery, adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, post-cardiopulmonary bypass syndrome, autoimmune disorders, pancreatitis, vasculitis, anaphylaxis, or drug overdose. SIRS can lead to organ failure, shock, and death. ***(Neviere, 2016)***