Effect of Statins in Early Sepsis

An Essay

By
Amr Shawky Khaleifa Salman
M.B., B.Ch.

Supervisors

Prof. Naglaa Mohammad Ali El Sayed
Professor of anaesthesia and ICU
Faculty of Medicine - Ain Shams University

Ass. Prof. Ayman Anise Metry Saied
Assistant professor of Anaesthesia and ICU
Faculty of medicine - Ain Shams University

Dr. Ayman Ibrahim Tharwat
Lecturer of Anaesthesia and ICU
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2014

سورة البقرة الآية: ٣٢

Acknowledgement

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

Really I can hardly find the words to express my gratitude to ***Prof. Naglaa Mohammad Ali El Sayed****, Professor of anaesthesia and ICU, Faculty of Medicine - Ain Shams University, for her supervision, continuous help, encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work. It is a great honor to work under her guidance and supervision.*

I would like also to express my sincere appreciation and gratitude to ***Ass. Prof. Ayman Anise Metry Saied,*** *Assistant professor of anaesthesia and ICU, Faculty of Medicine - Ain Shams University, for his continuous directions and support throughout the whole work.*

I feel deeply thankful to ***Dr. Ayman Ibrahim Tharwat****, Lecturer of anaesthesia and ICU, for his continuous unlimited help, unlimited patience and close supervision throughout the entire work.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Amr Shawky Khaleifa Salman

Contents

List of Abbreviations

AKI	:	Acute kidney injury
AKIN	:	Acute Kidney Injury Network
ALI	:	Acute lung injury
APACHE	:	Acute Physiologic and Chronic Health Evaluation
APC	:	Activated protein C
ARDS	:	Acute respiratory distress syndrome
CRP	:	C-reactive protein
CYP450	:	Cytochrome P450 enzyme
DIC	:	Disseminated intravascular coagulation
HMG-CoA reductase	:	3-hydroxyl-3-methylglutaryl CoA reductase
HPS	:	Heart Protection Study
ICU	:	Intensive care unit
ISRCT	:	International scientific randomized controlled trial
LDL	:	Low-Density Lipoprotein
LPS	:	Lipopolysacharide
MAPK	:	Mitogen-activated protein kinase
MCP1	:	Monocytic chemoattractant protein 1
NCT	:	National controlled trial
NFκB	:	Nuclear factor kappa B
NOS	:	Nitric oxide synthase

List of Abbreviations (Cont.)

PAI	:	Plasminogen activator inhibitor
PI3K	:	Phosphatidyinositol-3 kinases
PPARs	:	Peroxisome proliferator-activated receptors
RCT	:	Randomized controlled trials
RIFLE	:	Risk/Injury/Failure/Loss/End-Stage Renal Disease
RRT	:	Renal replacement therapy
SIRS	:	Systemic inflammatory response syndrome
SOFA	:	Sequential Organ Failure Assessment
SVR	:	Systemic vascular resistance
Th cell	:	T-helper cell
TNF	:	Tissue necrosis factor
VAP	:	Ventillator associated pneumonia
VWF	:	Von Willebrand factor

List of tables

List of Figures

Introduction

Sepsis defined by consensus conference as "the systemic inflammatory response syndrome during infection" ***(Hotchkiss and Karl, 2003),*** is generally viewed as a disease aggravated by the inappropriate immune response encountered in the infected individuals.

Severe sepsis and septic shock are common and frequently fatal. A future challenge may be to test both the efficacy and the safety of statins when administered at the onset of sepsis and in patients with severe sepsis or septic shock admitted into intensive care unit. ***(Remick, 2007).***

The pathophysiological process, signs and symptoms of sepsis are important to be discussed for understanding the role of statins. Infection, sepsis, severe sepsis, and multi-organ dysfunction have internationally recognized definitions. ***(Cohen, 2002).***

Hospital mortality rate of severe sepsis remains between 30% and 50%, or 500000 deaths per year (1400 each day) worldwide, with as many deaths annually as those from acute myocardial infarction and the number is projected to grow. ***(Annane et al., 2002).***

As the mortality of severe sepsis remains unacceptable, much research for therapeutic interventions is done to improve outcomes.

Considerable amount of research have been targeted to clarify the mechanisms of sepsis. With the exception of activated protein C, no therapy targeting the inflammatory cascade has been shown to alter mortality in sepsis.

The ideal agent would be cheap, have a clearly established and minimal side effect profile, multiple modes of delivery, and have a pleiotropic effect upon the inflammatory cascade. ***(Bernard et al., 2001).***

How close statins come to this ideal is the target. Statins therapy may be the next logical step in the search of adjuvant therapy. ***(Almog et al., 2004).***

Aim of the work

The aim of our study to explain the anti-inflammatory and pleiotropic effect of statin as an adjunctive therapy in early sepsis, to determine whether patients with early sepsis treated with statin develop severe sepsis less frequently or not, to evaluate the impact of statin therapy on duration of ICU-stay and patient outcome and need for organ supportive measures.

Pathophysiology of Sepsis

Sepsis syndrome results from a host reaction to infection, which includes a systemic inflammatory response, enhanced coagulation, and impaired fibrinolysis. The systemic inflammatory response syndrome (SIRS) is defined by fever or hypothermia, tachycardia, tachypnea, and leukocytosis, leukopenia, or the presence of immature neutrophil. **(Hotchkiss, 2003).**

SIRS can result from numerous conditions but only becomes "sepsis" when infection is etiologic. When sepsis causes at least one organ dysfunction, the syndrome is termed "severe sepsis," and sepsis-induced hypotension that is refractory to fluid challenge defines "septic shock." **(Bone, 1992).**

Table (1): Definitions related to sepsis

Term	Definition and Criteria
Infection	Microorganism invasion of a normally sterile site
Bacteremia	Presence of viable microorganisms in the blood
Systemic Inflammatory Response Syndrome (SIRS)	A systemic inflammatory response to a pathologic insult, such as a burn, trauma, pancreatitis, or infection. SIRS requires two or more of the following conditions: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg • WBC >12,000/mm^3, <4000 cells/mm^3, or >10% immature (band) forms
Sepsis (= 1 + 3)	The syndrome caused by a systemic inflammatory response secondary to infection
sepsis-induced Hypotension,	A decrease in systolic blood pressure <90 mm Hg, a mean arterial pressure <60 mm Hg, or a reduction of >40 mm Hg from baseline

Term	Definition and Criteria
Severe sepsis	Sepsis associated with organ dysfunction. Specific organ dysfunctions include, but are not limited to, hypotension, renal dysfunction, respiratory failure, and altered mental status.
Septic shock (= 5+ 7)	Sepsis with hypotension or hypoperfusion despite adequate fluid resuscitation.

(Cohen, 2002)

While the SIRS criteria are sensitive for septic patients, they are criticized for lacking specificity. Many, if not most, ICU patients have tachypnea and tachycardia, raising doubt as to the diagnostic utility of the SIRS criteria. **(Vincent**, **2006).**

Although the specificity of SIRS is increased by requiring three of the criteria, or by mandating that one of two required criteria be abnormal temperature or white blood cell count, even two criteria maintain prognostic importance. **(Brun-Buisson , 2000).**

Prevalence of sepsis

Large epidemiologic studies report an incidence of 1 to 3 cases per 1000 population per year resulting in approximately 750,000 cases annually in the United States. The average sepsis survivor requires 7 to 14 days of intensive care unit (ICU) support with much of this time spent on a ventilator. After ICU discharge, an additional 10- to 14-day hospital stay is typical. Thus, the average hospital length of stay for survivors is 3 to 5 weeks. **(Martin et al., 2003).**

Hospital charges in excess of tens of thousands of dollars are common for individual patients, resulting in annual U.S. expenditures of nearly $17 billion. The hospital mortality rates remain unacceptably high; 30% to 40% of patients die despite prompt, comprehensive treatment **(Angus et al., 2001).**

Predictors of worse outcomes include advanced age, cancer, and a hypothermic presentation. Historically, it was believed specific characteristics of the invading pathogen determined prognosis, but recent investigations have undermined this long-held belief. The identity of the infecting organism is of lesser consequence than physiologic derangements provided appropriate, prompt antimicrobial therapy is administered **(Martin et al., 2006).**

At the bedside, the best practical predictor of outcome is simply the number of organ systems with sepsis-induced dysfunction. Each new organ system failure adds roughly 15% to 20% risk of death to the baseline 10% to 15% mortality rate seen among ICU patients.

On average, patients have two or three failing organ systems at the time of diagnosis. **(Levy et al., 2005).**

Septic patients present typically in their sixth or seventh decade of life, and the average age of afflicted patients has increased consistently over time. For unclear reasons, males are affected more commonly**(Bernard et al., 2004).**

Although the condition can occur in previously healthy individuals, it is more common in patients with chronic diseases, particularly the immunocompromised. Occurrence rates are higher in those with diabetes mellitus, malignancy, chronic immune suppressive therapy, or human immunodeficiency virus infection. Patients with disrupted skin, especially trauma victims or surgical patients, are also more likely to develop severe sepsis **(Vincent et al., 2003).**

Sepsis has no definitive age, gender, racial, or geographic boundaries. **(Dombrovskiy et al., 2007).**

In addition to the number of malfunctioning organs, the severity of organ dysfunction also correlates with outcome.

For example, the need for higher or escalating vasoactive medication doses is associated with a worse prognosis than lower dose requirements or no requirement at all. **(Ferreira et al., 2001).**

Likewise, increasing levels of renal dysfunction, as measured by either the Risk/Injury/Failure/Loss/End-Stage Renal Disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria, are also prognostic, including degrees of creatinine elevation thought to be unimportant. **(Mehta et al., 2007).**

Several severity of illness scores have been developed based on assessment of organ functions, including the Acute Physiologic and Chronic Health Evaluation (APACHE) system and the Sequential Organ Failure Assessment (SOFA). These scoring systems are best used as tools to compare severity of illness in large study populations and have less utility as prognostic tools for individual patients. **(Lemeshow et al., 1995).**

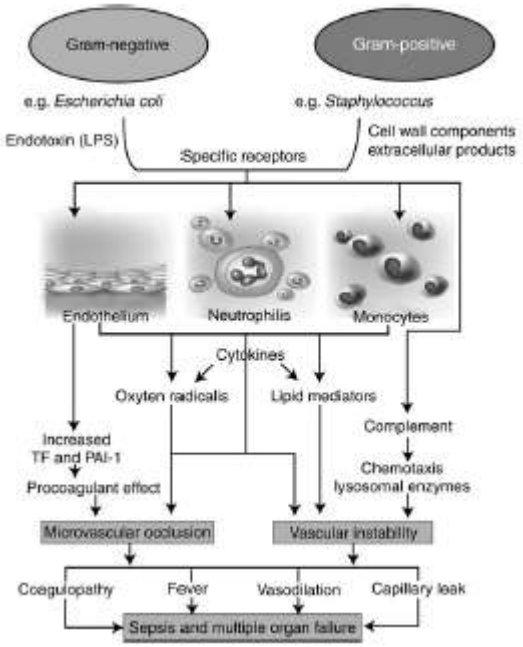

Fig. (1): Pathophysiology of sepsis and multi-organ failure ***(adopted from Cohen et al., 2002)***