Early Versus Late Norepinephrine Therapy in Management of Septic Shock as Prognostic Factor of Mortality

A Thesis

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Hussein Hassan Ibrahim

List of Contents

List of Abbreviations

Abb.	Meaning
ARDS	Acute respiratory distress syndrome
NLRs	Nucleotide-binding oligomerization domain–like receptors
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
TNF-α	Tumor Necrosis Factor Alpha
PPIs	Proton pump inhibitors
AKI	Acute kidney injury
ALI	Acute lung injury
APACHE	Acute Physiology and Chronic Health Evaluation
ACTH	Adrenocorticotropic hormone
VTE	Against venous thromboembolism
CNS	Central nervous system
CVP	Central venous pressure
CLRs	C-type lectin receptors
EGDT	Early goal-directed therapy
GI	Gastrointestinal
H2RAs	Histamine-2 receptor antagonists
LV	Left ventricular
LMWH	Low-molecular-weight heparin
MRSA	Methicillin-resistant Staphylococcus aureus
NETs	Neutrophil extracellular traps

Abb.	Meaning
NO	Nitric oxide
PAMPs	Pathogen-associated molecular patterns
PAI-1	Plasminogen activator inhibitor type 1
PBW	Predicted body weight
PD-1R	Programmed death-1 receptor
PAR1	Protease activated receptor 1
PA	Pulmonary artery
RLRs	Retinoic acid inducible gene 1–like receptors
SAD	Sepsis- associated delirium
SE	Septic encephalopathy
S1P1	Sphingosine-1 phosphate receptor 1
TLRs	The endosome
TM	Thrombomodulin
TLRs	Toll-like receptors
UFH	Unfractionated heparin
VE	Vascular endothelial
$ScvO_2$	Venous oxygen saturation
VAP	Ventilator-associated pneumonia

List of Tables

List of Figures

Introduction

Sepsis is a clinical syndrome of life-threatening organ dysfunction caused by a dysregulated response to infection. In septic shock, there is a critical reduction in tissue perfusion; acute failure of multiple organs, including the lungs, kidneys, and liver. Common causes include many different species of gram-positive and gram-negative bacteria. Immunocompromised patients may have uncommon bacterial or fungal species as a cause. Signs include fever, hypotension, oliguria, and confusion. Diagnosis is primarily clinical combined with culture results. Early recognition and treatment is critical. Treatment is aggressive fluid resuscitation, antibiotics, surgical excision of infected or necrotic tissue and drainage of pus, and supportive care ***(Singer et al., 2016).***

Early goal-directed therapy provided significant benefits with respect to outcomes for septic shock patients. However, massive fluid resuscitation may increase extravascular edema, aggravate pulmonary dysfunction and compromise tissue oxygenation. Therefore, investigating the rational use of vasopressors in septic shock is very important. Thus far, most studies have focused on the rational use of different types of vasopressors ***(Daley et al., 2013).***

The third edition of the guidelines for management of severe sepsis and septic shock also concentrates on the choice of vasopressors. The guidelines recommend that vasopressors (norepinephrine as the first choice) be administered for hypotension refractory to initial fluid resuscitation and to maintain a mean arterial pressure (MAP) ≥65 mm Hg ***(Dellinger et al., 2012).***

However, it is the timing of vasopressor therapy, rather than the specific agent, that appears to be crucial ***(Parrillo et al., 2008).***

Aim of the Work

Demonstration of the relationship between delay in initiation of vasopressor therapy (norepiniphrine) in the management of septic shock patients and the mortality rate. Determine effects of early Norepinephrine administration on septic shock patients and their ICU length of stay.

Pathophysiology of Septic Shock

Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. *Septic shock* is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality. History of classification included: Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). Severe sepsis occurs as a result of both community-acquired and health care–associated infections. Pneumonia is the most common cause, accounting for about half of all cases, followed by intraabdominal and urinary tract infections ***(Seymour et al., 2016).***

Blood cultures are typically positive in only one third of cases, and in up to a third of cases, cultures from all sites are negative. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common gram-positive isolates, whereas *Escherichia coli*, klebsiella species, and *pseudomonas aeruginosa*predominate among gram-negative isolates ***(Ranieri et al., 2012).***

In study involving 14,000 ICU patients in 75 countries, gram-negative bacteria were isolated in 62% of patients with severe sepsis who had positive cultures, gram-positive bacteria in 47%, and fungi in 19% ***(Vincent et al., 2009).***

Risk factors for severe sepsis are related both to a patient's predisposition for infection and to the likelihood of acute organ dysfunction if infection develops. There are many well-known risk factors for the infections that most commonly precipitate severe sepsis and septic shock, including chronic diseases (e.g., the acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, and many cancers) and the use of immunosuppressive agents. Among patients with infections, the risk factors for organ dysfunction are less well studied but probably include the causative organism and the patient's genetic composition, underlying health status, and preexisting organ function, along with the timeliness of therapeutic intervention. Age, sex, and race or ethnic group all influence the incidence of severe sepsis, which is higher in infants and elderly persons than in other age groups, higher in males than in females, and higher in blacks than in whites ***(Mayr et al., 2010).***

Clinical Features

The clinical manifestations of sepsis are highly variable, depending on the initial site of infection, the causative organism, the pattern of acute organ dysfunction, the underlying health status of the patient, and the interval before initiation of treatment. The signs of both infection and organ dysfunction may be subtle, and thus the most recent international consensus guidelines provide a long list of warning signs of incipient sepsis:

Sepsis (documented or suspected infection plus ≥1 of the following)†

General variables

- Fever (core temperature, >38.3°C)
- Hypothermia (core temperature, <36°C)
- Elevated heart rate (>90 beats per min or >2 SD above the upper limit of the normal range for age)
- Tachypnea
- Altered mental status
- Substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-hr period)
- Hyperglycemia (plasma glucose, >120 mg/dl [6.7 mmol/liter]) in the absence of diabetes

Inflammatory variables

- Leukocytosis (white-cell count, >12,000/mm^3)
- Leukopenia (white-cell count, <4000/mm^3)
- Normal white-cell count with >10% immature forms
- Elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range)
- Elevated plasma procalcitonin (>2 SD above the upper limit of the normal range)

Hemodynamic variables

- Arterial hypotension (systolic pressure, <90 mm Hg; mean arterial pressure, <70 mm Hg; or decrease in systolic pressure of >40 mm Hg in adults or to >2 SD below the lower limit of the normal range for age)
- Elevated mixed venous oxygen saturation (>70%)‡
- Elevated cardiac index (>3.5 liters/min/square meter of body-surface area)§

Organ-dysfunction variables

- Arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, <300)
- Acute oliguria (urine output, <0.5 ml/kg/hr or 45 ml/hr for at least 2 hr)
- Increase in creatinine level of >0.5 mg/dl (>44 μmol/liter)
- Coagulation abnormalities (international normalized ratio, >1.5; or activated partial-thromboplastin time, >60 sec)
- Paralytic ileus (absence of bowel sounds)
- Thrombocytopenia (platelet count, <100,000/mm^3)
- Hyperbilirubinemia (plasma total bilirubin, >4 mg/dl [68 μmol/liter])

Tissue-perfusion variables

- Hyperlactatemia (lactate, >1 mmol/liter)
- Decreased capillary refill or mottling

Severe sepsis (sepsis plus organ dysfunction)

Septic shock (sepsis plus either hypotension [refractory to intravenous fluids] or hyperlactatemia)¶

Figure (1): Diagnostic Criteria for Sepsis, Severe Sepsis, and Septic Shock ***(Seymour et al., 2016).***

Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory compromise is classically manifested as the acute respiratory distress syndrome (ARDS), which is defined as hypoxemia with bilateral infiltrates of noncardiac origin ***(Ranieri et al., 2012).***

Cardiovascular compromise is manifested primarily as hypotension or an elevated serum lactate level. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors, and myocardial dysfunction may occur. The brain and kidneys are also often affected. Central nervous system dysfunction is typically manifested as obtundation or delirium. Imaging studies generally show no focal lesions, and findings on electroencephalography are usually consistent with nonfocal encephalopathy. Critical illness polyneuropathy and myopathy are also common, especially in patients with a prolonged ICU stay. Acute kidney injury is manifested as decreasing urine output and an increasing serum creatinine level and frequently requires treatment with renal-replacement therapy. Paralytic ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular