The Effect of Low Dose Dexamethazone Therapy on The Expression of Macrophage Migration Inhibitory Factor in Critically Ill Children With Septic Shock

Thesis

Submitted For Partial Fulfillment of Master Degree ***In***

Pediatrics

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Introduction

Septic shock is a serious medical condition caused by decreased tissue perfusion and oxygen delivery as a result of infection and sepsis, though the microbe may be systemic or localized to a particular site. It can cause multiple organ failure and death. Critically ill children are the most common victims of septic shock, as their immune systems cannot deal with the infection effectively. The mortality rate from septic shock is approximately 50% ***(Kumar et al., 2007)***.

Sepsis and septic shock are very common conditions among critically ill patients that lead to multiple organ dysfunction syndrome (MODS) and death ***(Domingos et al., 2007)***.

Recent studies demonstrated that macrophage migration inhibitory factor (MIF) functions as initiator of inflammation by regulation of a number of pro-inflammatory cytokines, including TNF-α,IL-1 and IL-6. More over, MIF is essential for T-cell activation and is expressed dominantly in activated Th2 cells ***(ILLei and Lipsky, 2004)***.

Glucocorticoids have broad anti-inflammatory and regulatory effects on the host immune response. They reduce the production of numerous mediators of inflammation, including proinflammatory cytokines, prostaglandins, and reactive oxygen and nitrogen species. Glucocorticoids decrease leukocyte migration to sites of inflammation by inhibiting the expression of adhesion molecules, and they

promote apoptosis of leukocytes, thereby limiting the magnitude of the inflammatory response. Although the clinical impact of glucocorticoids on disease progression is variable, their influence on the signs and symptoms of severe inflammation, especially in the short term, is often life saving ***(Harry et al., 2007)***.

Aim of the Work

Our aim is to study the effect of exogenous corticosteroid therapy on MIF expression in pediatric critically ill patients with Septic shock and the relation to the morbidity and mortality.

Septic Shock

Septic shock is a serious medical condition caused by decreased tissue perfusion and oxygen delivery as a result of infection and sepsis, though the microbe may be systemic or localized to a particular site. It can cause multiple organ failure and death. Critically ill children are the most common victims of septic shock, as their immune systems cannot deal with the infection effectively. The mortality rate from septic shock is approximately 50% (***Kumar et al., 2007)***.

One of the most frequent and serious problem that clinicians face is the management of serious infections that trigger a systemic inflammatory response, termed 'septicemia'. When sepses results in hypotension and organ dysfunction, it is referred to as 'septic shock'. Septic shock is the most common cause of death in intensive care units. In the USA alone it is estimated that more than 100000 deaths occur each year due to septicemia and septic shock ***(Parrillo, 1993).***

Despite advances in the supporting care, sepsis and septic shock are now among the most common causes of death in pediatric ICU ranging from 20-66 % ***(Balk, 2000).***

Definition of septic shock

To diagnose septic shock, the following two criteria must be met:

1. Evidence of infection, through a positive blood culture.
2. Refractory hypotension - hypotension despite adequate fluid resuscitation and cardiac output.
    - In adults it is defined as a systolic blood pressure<90 mmHg, or a MAP<60mmHg, without the requirement for inotropic support, or a reduction of 40 mmHg in the systolic blood pressure from baseline.

- In children it is BP<2 SD of the normal blood pressure.

In addition to the two criteria above, two or more of the following must be present:

- Tachypnea (high respiratory rate) > 20 breaths per minute or, on blood gas, a P_aCO_2 less than 32 mmHg.
- White blood cell count<4000 cells/mm³ or>12000 cells/mm³ (<$4x10^9$ or> 12 x 10^9 cells/L)***(Tslotou et al,2005).***

Table (1): Definitions

1. ***Infection:*** Microbial phenomenon characterized by at inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
2. Bacteremia: The presence of viable bacteria in the blood.
3. Systemic inflammatory response syndrome: The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:
   a. Temperature > 38°C or < 36°C
   b. Heart rate > 90 beats /min
   c. Respiratory rate > 20 breaths/min or Paco2 < 32 for(<4.3kPa).
   d. WBO 12.000 cells/mm3, <4000 cells/mm3, or > 10% immature (band) forms.
4. ***Sepsis:*** The systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection: a. Temperature >38°C or <36°C b. Heart rale > 90 beats/min c. Respiratory rate > 20 breaths/min or Paco2 < 32 for (4.3kPa).
   d. WBC > 12.000 cells/mm3, < 4000 cells/mm3, or > 10% immature (band) forms.
5. Severe Sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
6. Early septic shock : Clinical diagnosis of sepsis syndrome plus hypotension (systolic blood pressure below 90 mmHg or 40 mmHg decrease blow baseline systolic blood pressure) that lasts for less than 1 hour

and is responsive to conventional therapy (intravenous fluid administration or pharmacological intervention).

7. Refractory septic shock: Clinical diagnosis of sepsis syndrome, plus hypotension (systolic blood pressure below 90 mmHg or a 40 mmHg decrease below baseline systolic blood pressure) that lasts for more than 1 hour despite adequate volume resuscitation and that requires vasopressors or higher doses of dopamine (> 6 ug/kg).
8. Multiple organ dysfunction syndrome: Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

(Bone, 1991).

Frequency

The overall frequency of septic shock was 8.2 per 100 ICU admissions. Its annual frequency significantly increased from 7.0 in 1993 to 9.7 per 100 ICU admissions in 2000 ***(Djillali et al., 2003)***.

Table (2): Sepsis in the United States

Sepsis in the United States			
Category	Number of Cases	Crude Mortality (%)	Number of Deaths Annually
Sepsis	400,000	15	60,000
Severe sepsis (sepsis plus organ failure)	300,000	20	60,000
Septic shock (severe sepsis plus refractory hypotension)	200,000	45	90,000

(Wenzel RP, 2002)

Pathophysiology

The septic response was once believed to be simply exaggerated inflammation. The last decade has brought to light a major conceptual advance. Sepsis pathophysiology is very complex and remains incompletely understood, but clearly involves inflammatory, procoagulant, antifibrinolytic, and microvascular components ***(Sakr,2004)***.

The pathophysiology of septic shock is not precisely understood, but it involves a complex interaction between the pathogen and the host's immune system. The normal physiologic response to localized infection includes the activation of host defense mechanisms that result in the influx of activated neutrophils and monocytes, the release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of coagulation pathways. These mechanisms are in play during septic shock but on a systemic scale, leading to diffuse endothelial disruption, vascular permeability, vasodilation, and thrombosis of end-organ capillaries.

The cascade of inflammation and thrombosis can be triggered by endotoxins contained within the cell wall of gram-negative bacteria or exotoxin released by gram-positive bacteria. Endothelial damage itself can further activate inflammatory and coagulation cascades, creating in effect a positive feedback loop, and leading to further endothelial and end-organ damage.

As a result of these interactions, immune cellular activation occurs with the release of cytokine and noncytokine mediators. The most common inflammatory mediators associated with sepsis are tumor necrosis factor-alpha (TNF-alpha), interleukin 1 (IL-1), and interleukin 6 (IL-6), all implicated in the diffuse activation of a systemic inflammatory response. Mediators with vasodilatory and endotoxic

properties are also released systemically, including prostaglandins, thromboxane A2, and nitric oxide. This results in vasodilation and endothelial damage, which leads to hypoperfusion and capillary leak. In addition, cytokines activate the coagulation pathway, resulting in capillary microthrombi and end-organ ischemia ***(Nguyen et al.,2006)***.

Septic shock falls under the category of distributive shock, which is characterized by pathologic vasodilation and shunting of blood from vital organ to nonvital tissues such as skin, skeletal muscle, and adipose. The mechanisms implicated in this pathologic vasodilation are multifactorial, but primary factors are thought to be (1) activation of ATP-sensitive potassium channels in vascular smooth muscle cells and (2) activation of nitric oxide synthase. K-ATP channels are directly activated by lactic acidosis. Nitric oxide (NO) also activates potassium channels. Potassium efflux from cells results in hyperpolarization, inhibition of calcium influx, and vascular smooth muscle relaxation ***(Landry and Oliver,2001)***.

Endothelial dysfunction and vascular maldistribution of distributive shock results in global tissue hypoxia or inadequate delivery of oxygen to vital tissues. In addition, mitochondria can become dysfunctional, thus compromising oxygen utilization at the tissue level. Furthermore, activation of the coagulation cascade and fibrin deposition cause microthombi to form in end-organ capillaries. These factors lead to organ dysfunction and eventual failure ***(Trzeciak and Rivers, 2005)***.

Local inflammation and substances elaborated from organisms, especially endotoxin, activate neutrophils, monocytes, and tissue macrophages. This results in a cascade of proinflammatory and anti-inflammatory cytokines and other mediators, such as IL-1, IL-8, IL-10, tumor necrosis factor-alpha, prostaglandin E_1, endogenous corticosteroids, and catecholamines. Effects of this complex mediator cascade

include cellular chemotaxis, endothelial injury, and activation of the coagulation cascade. An imbalance in favor of anti-inflammatory cytokines may result in relative immunosuppression and, if persistent, in increased risk of death ***(Bone,1996)***.

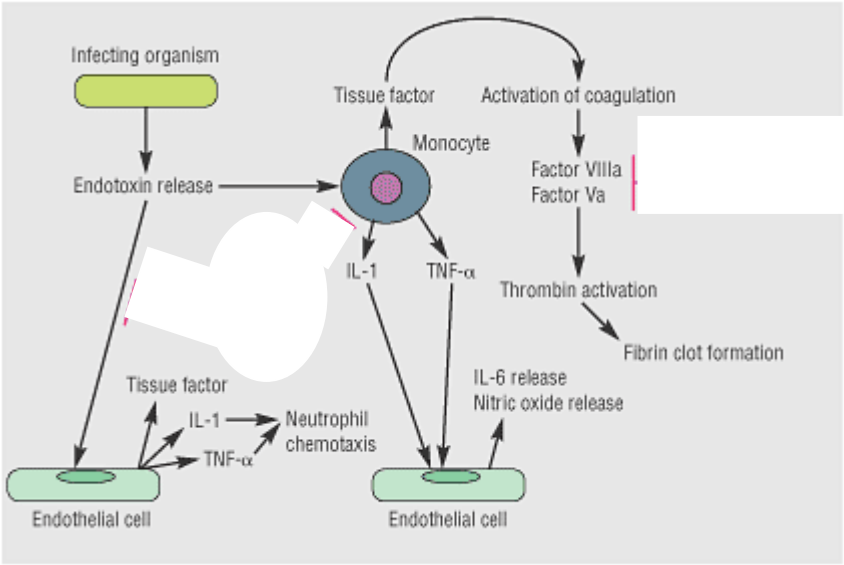

Fig. (1): Events associated with major of cytokins cascade in septic shock. Endotoxin and other antigenic components of infecting organism stimulate monocytes and local endothllal cells, resulting in elaboration of IL-1 tumor tactor-α (INF-α), and tissue factor (primary stimulant for coagutation cascade).

A series of pathogenic events are responsible for the transition from sepsis to severe sepsis/septic shock. The initial reaction to infection is a neurohumoral, generalized pro- and anti-inflammatory response. This begins with a cellular activation of monocytes, macrophages, and neutrophils that interact with endothelial cells through numerous pathogen rcognition receptors ***(Beutler,2004)***.

A further host response includes the mobilization of plasma substances as a result of this cellular activation and endothelial disruption. These plasma substances include cytokines such as tumor necrosis factor, interleukins, caspase,

proteases, leukotrienes, kinins, reactive oxygen species, nitric oxide, arachidonic acid, platelet activating factor, and eicosanoids. Activation of the complement and coagulation cascades further amplifies this elaborate chain of events ***(Haeney,1998)***.

The vascular endothelium is the predominant site of these interactions, and, as a result, there is microvascular injury, thrombosis, and a loss of endothelial integrity (capillary leak), resulting in tissue ischemia. This diffuse endothelial disruption is responsible for the various organ dysfunctions and global tissue hypoxia that accompany severe sepsis/septic shock ***(Aird, 2003).***

Table (3) Mediators of Sepsis

Type	Mediator	Activity
Cellular mediators	Lipopolysaccharide	Activation of macrophages, neutrophils, platelets, and endothelium releases various cytokines and other mediators
	Lipoteichoic acid	
	Peptidoglycan	
	Superantigens	
	Endotoxin	
Humoral mediators	Cytokines	Potent proinflammatory effect
	TNF-alpha and IL-1 b	Neutrophil chemotactic factor
	IL-8	Acts as pyrogen, stimulates B and T lymphocyte proliferation, inhibits cytokine production, induces immunosuppression
	IL-6	
	IL-10	
	MIF*	Activation and degranulation of neutrophils
	G-CSF	Cytotoxic, augments vascular permeability, contributes to shock
	Complement	Involved in hemodynamic alterations of septic shock
	Nitric oxide	
	Lipid mediators	Promote neutrophil and macrophage, platelet activation and chemotaxis, other proinflammatory effects
	Phospholipase A2	
	PAF†	Enhance vascular permeability and contributes to lung injury
	Eicosanoids	
	Arachidonic acid metabolites	Enhance neutrophil-endothelial cell interaction, regulate leukocyte migration and adhesion, and play a role in pathogenesis of sepsis
	Adhesion molecules	
	Selectins	
	Leukocyte integrins	

*Macrophage inhibitory factor †Platelet activating factor

(Lorente et al., 1993)

Causes, incidence, and risk factors:

Septic shock occurs most often in the very old and the very young. It also occurs in people who have other illnesses.

Any type of bacteria can cause septic shock. Fungi and (rarely) viruses may also cause the condition. Toxins released by the bacteria or fungus may causetissue damage, and may lead to low blood pressure and poor organ function. Many researchers believe that abnormal blood clots in small arteries cause the lack of blood flow and poor organ function.

The toxins also cause a strong inflammatory response from the body, which contributes to septic shock.

Risk factors for septic shock include:

- Diabetes
- Diseases that weaken the immune system such as AIDS
- Lymphoma
- Leukemia
- Diseases of the genitourinary system, biliary system, or intestinal system
- Recent infection
- Long-term use ofantibiotics
- Recent surgery or medical procedure.

(Marx, 2002)

<u>Other risk factors of infection in critically ill patients:</u>

Many factors are known to increase the risk of nosocomial infection such as:

Table (4): Risk factors of infection in ICU

Malnutrition
Poor health care worker hygiene (handwashing)
Medications
Endotracheal intubation with mechanical ventilation
Diabetes mellitus
Catheters (type, location, duration, etc.)
Renal insufficiency
Skin breakdown i Radiation therapy Surgery
feranulocytopenia
Immunosuppresion (acquired i.e. HIV, drugs or primary inborn errors).

(Gary et al., 1998)

Diagnosis

To diagnose severe sepsis/septic shock as early as possible, its necessary to recognize historical, clinical, and laboratory findings that are indicative of infection, organ dysfunction, and global tissue hypoxia ***(Nguyen et al, 2006)***.

I. Historical

Both epidemiologic (e.g, contact risk for meningococcemia) and patient risk for infection must first be considered. The presence of immunocompromising conditions and prosthetic devices such as intravenous lines, heart valves, and urinary catheters increases infection risk. Focal findings of infection should be sought on medical history and physical examination.

II. Clinical

The early phases of septic shock may produce evidence of volume depletion, such as dry mucous membranes, and cool, clammy skin. After resuscitation with fluids, however, the clinical picture is typically more consistent with

hyperdynamic shock, including tachycardia, bounding pulses with a widened pulse pressure, a hyperdynamic precordium on palpation, and warm extremities. Signs of possible infection include fever, localized erythema or tenderness, consolidation on chest examination, abdominal tenderness, and meningismus. Signs of end-organ hypoperfusion include tachypnea, oliguria, cyanosis, mottling of the skin, digital ischemia, abdominal tenderness, and altered mental status. Often, a definitive diagnosis cannot be made on the basis of initial findings on history taking and physical examination, and treatment for several possible conditions commences simultaneously ***(Stephen et al.,2002).***

Clinical manifestations of septicemia:

Most of clinical signs and symptoms of sepsis are non specific.

1. Systemic manifestations:

They include fever often greater than 38°C and toxic appearance. It may be presented by hypothermia which has worse prognosis ***(Brun-Buisson et al., 2004).***

2. Neurological manifestations:

They may include irritability, lethargy, little interest in surroundings, poor eye contact with the examiner, hypotonia or hypertonia, weak cry and seizures ***(Brun-Buisson et al., 2004).***

3. Cardiovascular manifestations:

They may include tachycardia and poor peripheral perfusion, the blood pressure especially diastolic is slightly lower than that previously recorded ***(Parrillo, 2000).***