بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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Midodrine as adjunction support for Weaning off Norepinephrine in Septic Shock

Thesis

Submitted for Partial Fulfillment of Master Degree
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Hussien Gamal Mohammed Hafez

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List of Abbreviations

Abb.	Full term
BNP	B-Type Natriuretic Peptide
CRP	C-Reactive Protein
EGDT	Early goal-directed therapy
GD	Graves' Disease
GM-CSF	granulocyte-macrophage colony stimulating factor
HMGB-1	High mobility group box-1
ICAM1	Intercellular adhesion molecule 1
ICU	Intensive care units
IL-1ra	IL-1 receptor antagonist
IV	Intravenous
LFA1	Lymphocyte function-associated antigen 1
LOS	Length of stay
MAP	Mean arterial pressure
MIF	Migration inhibitory factor
MODS	Multiple organ dysfunction syndrome
MPO	Myeloperoxidase
NE	Norepinephrine
NF-κB	Nuclear Factor Kappa B
NK	Natural killer
NO	Nitric oxide
PAF	Platelet- activating factor
PAI-1	Plasminogen activator inhibitor 1
PAMPs	Pathogen-associated molecular patterns

PCT .....Procalcitonin

PGI2 .....Prostaglandin I2

PMN .....Polymorph nuclear

PRRs.....Pathogen recognition receptors

PSGL1 .....P-selectin ligand 1

ROS .....Reactive oxygen species

SD.....Standard deviation

SOFA.....Sepsis-related] Organ Failure Assessment score

SSC.....Surviving Sepsis Campaign

t1/2 .....The half-life

TFPI .....Tissue factor pathway inhibitor

TLR .....Toll-like receptors

TM .....Thrombomodulin

t-PA .....Tissue plasminogen activator

TXA2 .....Thromboxane A2

VE .....Vascular endothelial

INTRODUCTION

Sepsis, "life-threatening organ dysfunction caused by a dysregulated host response to infection." End organ damage is identified as an acute change in total Sequential [Sepsis-related] Organ Failure Assessment score (SOFA) ≥ 2 ***(Rhodes et al., 2016).*** Septic shock: A subset of sepsis "in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. These patients can be clinically identified by a vasopressor requirement to maintain a MAP ≥ 65mmHg and serum lactate < 2mmol/L in the absence of hypovolemia ***(Singer et al., 2016).*** Septic shock is the most challenging problem in critical care medicine and has a very high mortality, owing to the complex pathophysiology, the outcomes for septic shock patients remain disappointing ***(Dombrovskiy et al., 2007).*** 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 ***(Sandifer and Jones, 2013).***

The current 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 ***(LeDoux et al., 2000).*** Norepinephrine is a potent alpha-adrenergic agonist with minimal beta-adrenergic agonist effects. It can increase blood pressure successfully in patients with sepsis who remain hypotensive after fluid resuscitation. The dosage may

range from 0.2 to 1.5 µg/kg/min, and dosages as high as 3.3 µg/kg/min have been used because of the alpha-receptor down regulation in sepsis. In patients with sepsis, indices of regional perfusion (eg, urine flow) and lactate concentration have improved after norepinephrine infusion ***(Andre et al., 2020).*** The rate of weaning of Norepinephrine is usually an empirical choice made by the treating in critically ill patients. It is generally agreed that fluid resuscitation and Norepinephrine should be initiated promptly to treat shock and organ failure, and rapidly restore the mean arterial pressure (MAP) to 60 to 90 mmHg ***(Merouani et al., 2008).*** Midodrine is an orally available α1-adrenergic receptor agonist with alabelled indication for the treatment of symptomatic orthostatic hypotension ***(Wright et al., 1998).*** Its therapeutic effect is due to desglymidodrine, an active metabolite formed by enzymatic hydrolysis of midodrine. After oral administration, the prod rug reaches peak serum concentrations within 30 min and desglymidodrine reaches peak serum concentrations in 1 – 2 h ***(Wright et al., 1998).*** Due to midodrine's predictable pharmacologic response and favorable sympathomimetic effects in patients with orthostatic hypotension, it is utilized as an off-label treatment to provide hemodynamic support to facilitate the weaning of IV vasopressor infusions in ICU patients. The overall goal of midodrine administration is to minimize the adverse effects of IV vasopressors and decrease ICU length of stay ***(Poveromo et al., 2016).***

AIM OF WORK

This study aims to evaluate whether oral administration of midodrine is an effective adjunct to standard therapy to reduce the duration of IV norepinephrine and allow earlier discharge from ICU compared to control patients.

Chapter 1

SEPTIC SHOCK

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with septic shock being defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction that is associated with a higher rate of mortality ***(Shankar et al., 2016)***.

Septic shock is a result of a systemic response to infection or multiple infectious causes. The precipitating infections that may lead to septic shock if severe enough include but are not limited to appendicitis, pneumonia, bacteremia, diverticulitis, pyelonephritis, meningitis, pancreatitis, necrotizing fasciitis, MRSA and mesenteric ischemia ***(Gwon et al., 2012).***

It is a potentially fatal medical condition that occurs when sepsis, which is organ injury or damage in response to infection, leads to dangerously low blood pressure and abnormalities in cellular metabolism ***(Hotchkiss et al., 2016).***

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined septic shock ***(Singer et al., 2016).***

Proposed criteria for sepsis and septic shock

This proposal stems from the 2015 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3),