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Early vs Late Methylprednisolone in Acute Respiratory Distress Syndrome.

Thesis

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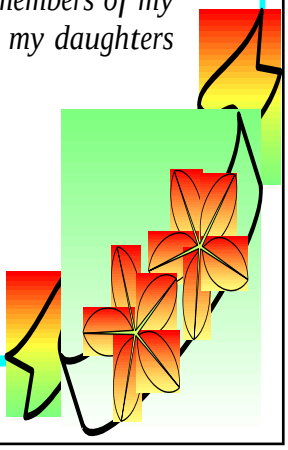

List of Contents

Page

List of Tables and Figures

Tables:

Figures:

List of Abbreviations

A

ABGs -------> arterial blood gases
ADP --------> adenosine di-phosphate
AECC ------> American–European Consensus Conference Committee
ALI ---------> acute lung injury
aPTT -------> activated partial thromboplastin time
ARDS ------> acute respiratory distress syndrome

B

BAL --------> bronchoalveolar lavage

C

CBG --------> corticosteroid-binding globulin
CCP --------> clara cell- specific protein
CINM ------> critical illness neuromyopathy
cmH_2O -----> centimeters of water
CMV -------> controlled mandatory ventilation
CO2 --------> carbon dioxide
COPD ------> chronic obstructive pulmonary disease
COX -------> cyclo-oxygenase
CPAP ------> continous positive airway pressure
CPB --------> cardiopulmonary bypass
CRP --------> C-reactive protein
CT ----------> computed tomography
CXR --------> chest x-ray

D

DAD -------> diffuse alveolar damage
DIC --------> disseminated intravascular coagulation
DM --------> diabetes mellitus
DNA ------> deoxyribonucleic acid

E

ECG ------> electrocardiogram
ECMO ---> extracorporeal membrane oxygenation
EIT -------> thoracic electrical impedance tomography
EN --------> enteral nutrition
EPA ------> eicosapentaenoic acid

ET-1 ------> endothelin 1

F

FDA ------> Food and Drug Administration
FDPs -----> fibrin degradation products
FFP -------> fresh frozen plasma
FiO2 ------> fraction of inspired oxygen
FRC -------> functional residual capacity

G

GC -------> glucocorticoid
GLA -----> γ-linolenic acid

H

Hb -------> haemoglobin
Hct ------> hematocrit
HFOV -----> high-frequency oscillatory ventilation
HMG-CoA-------> hydroxy-methylglutaryl-coenzyme
Hz -------> hertz

I

ICU -------> intensive care unit
IHD -------> ischemic heart diseases
IL ---------> interleukin
iNO ------> inhaled nitric oxide
INR ------> international normalized ratio

K

K ---------> Potassium
KL-6 -----> Krebs von den Lungen-6

L

LIS -------> lung injury score
LMWH -----> low molecular weight heparin
LPVS -----> lung-protective ventilatory strategy

M

MAP -----> mean arterial pressure
MIF ------> macrophage-inhibitory factor
mmHg ----> millimeters of mercury
MV -------> mechanical ventilation

N

Na --------> sodium
NAC -----> N-acetylcysteine
NIH ------> National Institutes of Health
NMBA -----> neuromuscular blocking agents
NO -------> nitric oxide
NS -------> non significant
NSAIDS -------> nonsteroidal anti-inflammatory drugs

O

OL-PEEP -------> open lung PEEP

P

P value ----> probability value
PAF -------> platelet-activating factor
PaO2 ------> partial pressure of arterial oxygen
PaO2/FiO2 ratio -------> partial pressure of arterial oxygen/fraction of inspired oxygen
PCO2 -------> partial pressure of arterial carbon dioxide
PEEP -------> positive end-expiratory pressure
PHV --------> permissive hypercapnic ventilation

Q

Q -------> cardiac output

R

RAGE -----> receptor for advanced glycation end products
RBC -------> red blood cells
RBS -------> random blood sugar
RCT -------> Randomized controlled trial
RM --------> recruitment maneuver
RNA -------> ribonucleic acid
RR ---------> Respiratory rate
rSPC ------> recombinant Surfactant Protein C–Based

S

SD ---------> Standard Deviation
SLE -------> systemic lupus erythromatosis
SPD -------> surfactant protein D
SpO2 -----> oxyhemoglobin saturation

T

TNF ------> tumor necrosis factor
TxA2 -----> thromboxane A2

V

V/Q -------> ventilation–perfusion ratio
VO2 ------> oxygen uptake
Vt ---------> tidal Volume

Early vs Late Methylprednisolone in Acute Respiratory Distress Syndrome

Marzouk M. Mervat, MD, El Said M. Amr, MD, Abd el Rahman A. Yasser, MD, Mansour A. Walid, MD,Abd el-salam S. Tamer, M.SC.

Abstract:

Introduction*: Acute respiratory distress syndrome (ARDS) is the clinical manifestation of severe acute lung injury. It is characterized by dyspnea, profound hypoxemia, diffuse bilateral infiltrates secondary to non-cardiogenic pulmonary edema on chest radiography, and decreased lung compliance. It occurs most frequently in the setting of sepsis, aspiration of gastric contents, trauma, or multiple transfusions. ARDS places a significant burden on the healthcare system, with an estimated prevalence of 7% of ICU admissions and hospital mortality rate of 50%.Pulmonary and systemic inflammations are the pathophysiologic hallmarks of this syndrome, and activation of the glucocorticoid receptor in pulmonary and circulating cells is an essential step in restoring homeostasis. Provision of supplemental oxygen, lung rest, and supportive care are the fundamentals of therapy. Acute respiratory distress syndrome frequently requires endotracheal intubation and mechanical ventilation. A low tidal volume and low plateau pressure ventilator strategy is recommended to avoid ventilator-induced injury. The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions.The aim of this study is to evaluate and compare the role of methylprednisolone in improvement of PaO2/FiO2 ratio, lung injury score, and reduction in C-reactive protein (CRP) in early and late phases of ARDS.*

Patients andmethods*: Our study was a prospective randomized study conducted in the department of ICU in Ain Shams University Hospitals. 90 patients with diagnosis of ARDSdefined by (the criteria ofBerlin definition) were randomly divided into two groups according tothe time of methylprednisolone protocol administration, group A received the protocol in early ARDS≤ 3days since diagnosis and group B received the protocol in late ARDS after7 days since diagnosis.*

Results*:Our study demonstrated that Methylprednisolone was effective in both early and late phases of ARDS with improvement in oxygenation (PaO2/FIO2 ratio), PEEP, CXR and LIS started at day 4 and reduction of CRP at day 5. But with superior and statistically more significant results (reduction in LIS ≥1 and successful extubation by day 7) in early ARDS when compared with Late ARDS. As regard, complications there was no statistically significant differences in MAP, RBS, serum sodium, serum potassium, GI bleeding nor new infection.*

Conclusion*: We conclude that the use of low-dose methylprednisolone provides evidence of efficacy in both early and late phases of ARDS with superior results in early ARDS plus no differences in adverse effects, when secondary prevention is implemented.*

References:

- ***Benjamin M P, Jonathan C, Guy D, Anthony S. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome. Crit Care Med 2009; 37: 1594 –1603.***
- ***Brun Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units: results from the ALIVE study. Intensive Care Med 2004; 30:51–61.***
- ***Kahdi F, Childs, Karim T. Acute Respiratory Distress Syndrome. Am Fam Physician 2003;67:315-22.***

Intoduction

Acute respiratory distress syndrome (ARDS) is the clinical manifestation of severe acute lunginjury. It is characterized by dyspnea, profound hypoxemia,diffuse bilateral infiltratessecondaryto noncardiogenic pulmonary edema on chest radiography, and decreased lung compliance. It occurs most frequently in the setting of sepsis, aspiration of gastric contents, trauma, or multiple transfusions (**Kahdi et al., 2003**).

ARDS places a significant burden on the healthcaresystem, with an estimated prevalence of 7%of ICU admissions and hospital mortality rate of 50% (**Brun et al., 2004).**

Pulmonary and systemicinflammation are the pathophysiologic hallmarks of this syndrome, and activation of the glucocorticoidreceptor in pulmonary and circulating cells is anessential step in restoring homeostasis (**Meduri et al., 2005)**.

In the early (<7 days) stages of ARDS, an exudative inflammation is thought to predominate. In later stages (>7 days), a fibroproliferative phase may

develop. Each of these two inflammatory phases has been considered potentially amenable to the anti-inflammatory effects of corticosteroid therapy (**Wajanaponsan et al.,2007**).

Provision of supplemental oxygen, lung rest, and supportive care are the fundamentals of therapy.Acute respiratory distress syndrome frequentlyrequires endotracheal intubation and mechanical ventilation. A low tidal volume and lowplateau pressure ventilator strategy is recommended to avoid ventilator-induced injury. (**Kahdi et al., 2003**).

The use of low-dose corticosteroids was associatedwith improved mortality and morbidity outcomes withoutincreased adverse reactions (**Benjamin et al.,2009**).