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**Early vs Late Methylprednisolone in Acute Respiratory
Distress Syndrome.**

Thesis

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Degree

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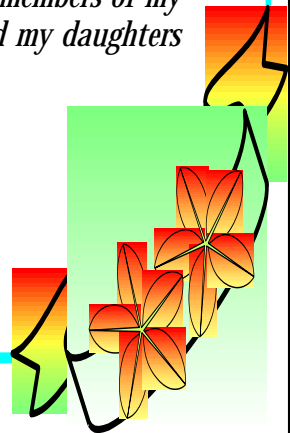
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List of Contents

Page

Acknowledgment	--
List of Abbreviations	I
List of Tables and Figures	V
* Introduction and Aim of the Work	1
* Review of Literature:	
· Chapter I: Acute Respiratory Distress Syndrome	4
· Chapter II: corticosteroids	43
* Patients and methods	60
* Results	71
* Discussion.....	96
* Summary.....	104
* Conclusion and recommendations	107
* References	108
* Arabic summary.....	

List of Tables and Figures

Tables:

Table 1: Lung injury score (Murray score) ----->**page 7**

Table 2: AECC criteria of ARDS -----> **page 8**

Table 3: Delphi definition of ARDS-----> **page 8**

Table 4: Berlin definition of ARDS -----> **page 9**

Table 5: Clinical Disorders Associated with the Development of Acute Respiratory Distress Syndrome (ARDS)-----> **page 10**

Table 6: Factors That Distinguish ARDS, CHF, and Pneumonia----->**page 20**

Table 7: NIH ARDS network protocol summary for low tidal volume ventilation -----> **page 30**

Table 8: Properties, dosing equivalents and therapeutic indications of systemic corticosteroids, relative to hydrocortisone-----> **page 45**

Table 9: Primary effects of glucocorticoids-----> **page 47**

Table 10: Trials of corticosteroids for Treatment of ARDS--
-----> **page 56**

List of Tables and Figures

- Table 11:** Trials of corticosteroids for prevention of ARDS-
-----> **page 58**
- Table 12:** Age distribution (Results) -----> **page 71**
- Table 13:** Gender distribution(Results)----->**page72**
- Table 14:** Co-morbidities(Results) -----> **page 72**
- Table 15:** Cause of ARDS(Results)-----> **page 72**
- Table 16:** PaO₂/FIO₂ ratio(Results) -----> **page 75**
- Table 17:** Positive end expiratory pressure (PEEP) in
cmH₂O(Results)-----> **page 77**
- Table 18:** Chest X-Ray score (No. of quadrants
infiltration)(Results) -----
--> **page 79**
- Table 19:** Lung injury score(Results) -----> **page 81**
- Table 20:**CRP in mg/dl(Results) -----> **page 83**
- Table 21:** LIS reduction ≥ 1 by day 7(Results) ---> **page 85**
- Table 22:** Extubation day(Results) -----> **page 85**
- Table 23:**Mean arterial pressure (MAP) in mmHg(Results) -
-----> **page 86**

Table 24: Random Blood Sugar (RBS) in mg/dl(Results)-----
-----> **page 88**

Table 25: Serum Sodium level in mEq/l(Results) -----
-----> **page 90**

Table 26: Serum Potassium level in mEq/l(Results) -----
-----> **page 92**

Table 27: Infection Survey(Results) -----> **page 94**

Figures:

Figure 1: The normal alveolus and the injured alveolus in
the acute phase of acute respiratory distress
syndrome-----
> **page 15**

Figure 2: Posterior-anterior (PA) CXR in patient with
ARDS-----> **page 21**

Figure 3: Chest CT scan evaluation of maximal recruitment
strategy and adequate PEEP titration in early severe
ARDS patient-----> **page23**

Figure 4: Pie chart shows etiology of ARDS ingroup A
(data presented as number of patients-----> **page 73**

Figure 5: Pie chart shows etiology of ARDS ingroup B (data presented as number of patients) -----> **page 74**

Figure 6: PaO₂/FIO₂ ratio(Results) -----> **page 76**

Figure 7: Positive end expiratory pressure (PEEP) in cmH₂O(Results) -----> **page 78**

Figure 8: Chest X-Ray score (No. of quadrants infiltration)(Results) -----
--> **page 80**

Figure 9: Lung injury score (Results) -----> **page 82**

Figure 10: CRP in mg/dl(Results) -----> **page 84**

Figure 11: Mean arterial pressure (MAP) in mmHg(Results) ----->
page 87

Figure 12: Random Blood Sugar (RBS) in mg/dl(Results) --
-----> **page 89**

Figure 13: Serum Sodium level in mEq/l(Results) -----
-----> **page 91**

Figure 14: Serum Potassium level in mEq/l(Results) -----
-----> **page 93**

List of Tables and Figures

Figure 15: GIT bleeding (number of patients)(Results) -----
-----> **page 94**

Figure 16: Infection Survey (number of patients
neg/pos)(Results) ----->
page 95

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
cmH₂O -----> 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

List of Abbreviations

T

TNF -----> tumor necrosis factor

TxA2 -----> thromboxane A2

V

V/Q -----> ventilation-perfusion ratio

VO₂ -----> oxygen uptake

V_t -----> 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 and methods: Our study was a prospective randomized study conducted in the department of ICU in Ain Shams University Hospitals. 90 patients with diagnosis of ARDS defined by (the criteria of Berlin definition) were randomly divided into two groups according to the time of methylprednisolone protocol administration, group A received the protocol in early ARDS ≤ 3 days since diagnosis and group B received the protocol in late ARDS after 7 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 lung injury. It is characterized by dyspnea, profound hypoxemia, diffuse bilateral infiltrates secondary to 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 healthcare system, with an estimated prevalence of 7% of ICU admissions and hospital mortality rate of 50% (**Brun et al., 2004**).

Pulmonary and systemic inflammation 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 (**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 frequently requires endotracheal intubation and mechanical ventilation. A low tidal volume and low plateau pressure ventilator strategy is recommended to avoid ventilator-induced injury. (**Kahdi et al., 2003**).

The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions (**Benjamin et al.,2009**).