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Original Article

A Clinico-pharmacological Study on Effect of Methylprednisolone in Acute Respiratory Distress Syndrome Patients

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Abstract

Background: Acute respiratory distress syndrome **(**ARDS) is as an acute condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the absence of evidence for cardiogenic pulmonary edema. The diagnosis is based on the ratio of the partial pressure of oxygen in the patient's arterial blood (PaO_2) to the fraction of oxygen in the inspired air (FiO_2); therefore, ARDS was defined by a PaO_2/FiO_2 ratio of <200, and in acute lung injury, it was <300. Late phase ARDS results due to inflammation and corticosteroids are considered as rescue therapy to improve oxygenation and hemodynamics in patients.

Aim of the Study: The aim of this study is to evaluate the effect of methylprednisolone in early ARDS in regard to outcome, incidence of infection, organ dysfunction, D-dimer, C-reactive protein (CRP), protein C, and protein S.

Materials and Methods: A total of 49 adult patients with ARDS were included. Group A patients (24) were administered methylprednisolone, and Group B patients (25) did not receive methylprednisolone. All the patients were diagnosed based on American-European Consensus Conference (AECC), Berlin and Kigali criteria for ARDS. History taking, clinical examination, radiological tests, blood investigations (CBC–LFT–RFT–electrolytes), arterial blood gase (ABG), serum lactate, international normalized ratio, fibrinogen, and aPTT, CRP, protein C, protein S, and D-dimer were undertaken before and after treatment with methylprednisolone.

Observations and Results: There were 49 patients with ARDS included in the study. The study group consisted of 24 (48.97%) patients, and the control group was 25 (51.02%) patients. 15 were males (62.32%) and 9 (37.50%) females in the study group. 16 were males (64%) and 9 females (36%) in the control group. The mean age in the study group was 44.12 ± 10.75, and the mean in the control group was 48.5 ± 11.26. Hospital-acquired Pneumonia (HAP), trauma, and community-acquired pneumonia (CAP) as the cause of ARDS were observed in 21.16%, 37.05%, and 33.33%, respectively, in the study group. The incidence of HAP, ,trauma and CAP was 32%, 32%, and 36%, respectively, in the control group.

Conclusions: Including methylprednisolone in addition to regular ventilator support and treatment protocol of ARDS patients, when used on first 7 days, improves the LIS, decreases the systemic inflammation, allows earlier extubation from mechanical ventilation, and decreases the incidence of hospital-acquired infection.

Key words: Acute lung injury, Acute respiratory distress syndrome, Hypoxia, Methylprednisolone, Oxygen saturation

INTRODUCTION

Since its first description, the acute respiratory distress syndrome (ARDS) has been acknowledged to be a major clinical problem in respiratory medicine.[1] International multicenter studies quote that ARDS is underdiagnosed and requires potential for improvement in its management. Predisposing factors such as exposure to high ozone levels and low Vitamin D plasma concentrations were found to be predisposing circumstances. Not only curative but also preventive strategies remain a major challenge since the two trials on aspirin and statins failed to reduce the incidence in at-risk patients.[1] The 1st week of treatment of ARDS with mechanical ventilation determines its pathophysiologic progression and its late phase effect on inflammation and disease outcome.[2] Use of the lung

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injury score (LIS) quantifying the physiologic respiratory impairment calculated by a 4-point score based on the levels of positive end-expiratory pressure (PEEP), ratios of PaO2 to fraction of inspired oxygen (FIO_2), the static lung compliance, and the degree of infiltration present on chest radiograph helps in decision making of treatment.[3] In patients in whom these LIS do not improve by the end of the 1st week and have persistent elevation in circulating levels of inflammatory cytokines and chemokines, markers of alveolocapillary membrane permeability[4] and fibrogenesis (dysregulated systemic inflammation)[2] also have a higher mortality.[5]

Glucocorticoids used in the 1st week of the treatment of ARDS help in downregulating the systemic inflammation which is associated with a significant clinical and oxygenation improvement with a reduced duration of mechanical ventilation and ICU length of stay.[6] Methylprednisolone was used in high doses during the 1st week of ARDS in many trials of patients with persistent pulmonary infiltrates, fever, and high oxygen requirement despite resolution of pulmonary or extrapulmonary infection. Pulmonary infection is usually assessed with bronchoscopy and bilateral bronchoalveolar lavage (BAL) and quantitative culture.[7] The present study was conducted with an aim to evaluate the effect of methylprednisolone when used in ARDS patients in regard to outcome, incidence of infection, organ dysfunction, D-dimer, C-reactive protein (CRP), protein C, and protein S.

Period of Study

The study duration was from August 2013 to July 2015.

Institution of Study

The study was conducted at Kannur Medical College, Anjarakandy, Kannur, Kerala.

Type of Study

This was a prospective, cross-sectional, and comparative study.

MATERILAS AND METHODS

A total of 49 adult patients with ARDS were included. Group A patients (24) were administered methylprednisolone and group B patients (25) did not receive methylprednisolone. All the patients were diagnosed based on the AECC, Berlin and Kigali criteria for acute respiratory distress syndrome (ARDS).[8] History taking, clinical examination, radiological tests, blood investigations (CBC–LFT–RFT–electrolytes), ABG, serum lactate, international normalized ratio, fibrinogen, and aPTT, CRP, protein C, protein S, and D-dimer were undertaken before and after treatment with methylprednisolone.

Inclusion Criteria

(1) Patients with ARDS criteria of AECC, (2) patients who are on ventilator, (3) patients in whom methylprednisolone was started within 48 h, and (4) patients aged above 18 years were included in this study.

Exclusion Criteria

(1) Patients with PaO2/FIO2 ratio more than 200 and (2) patients who were not on ventilators were excluded from the study. Once the diagnosis is established, IV methylprednisolone was given as loading dose 1 mg/kg body weight followed by 1 mg/kg/day from day 2 to day 14. The steroid was mixed in 240 mL of normal saline solution, and the rate of infusion was adjusted to 10mL/h. Methylprednisolone was given from day 15th to 21st 0.5 mg/kg/day and from day 22nd to 25th 0.25 mg/kg/day and from day 26th to 28th the dose was reduced to 0.125 mg/kg/day. In addition to ventilator support measures, patients in this study received low-molecular-weight heparin (40 mg of enoxaparin or 5,000 units of dalteparin subcutaneously per day) or low-dose, unfractionated heparin (5000 units subcutaneously twice daily) to prevent venous thromboembolism. In the absence of contraindication, ARDS patients received stress ulcer prophylaxis with an agent such as sucralfate 1 g (orally or through nasogastric tube 4 times daily), ranitidine (orally or through nasogastric tube twice daily, 50 mg intravenously every 6–8 h, or a 6.25 mg/h continuous intravenous infusion), or omeprazole (orally, intravenously, or through nasogastric tube daily). Patients also received nutritional support (enteral) within 24–48 h of admission to the ICU. From the day of admission to the Intensive Care Unit till the discharge, all the parameters were observed and the data collected were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

This was a prospective, cross-sectional comparative study conducted in a tertiary teaching hospital of Northern Kerala. 49 patients admitted in ICU diagnosed as ARDS based on the basis of AECC criteria, and laboratory investigations were included in the study. They were divided into two groups depending on the administration of IV methylprednisolone as mentioned in the materials and methods. The study group consisted of 24 (48.97%) patients and the control group was 25 (51.02%) patients. There were 15 males (62.32%) and 9 (37.50%) females in study group and 16 males (64%) and 9 females (36%) in the control group. The mean age in the study group was 44.12 ± 10.75, and the mean in the control group was 48.5 ± 11.26. Hospital-acquired pneumonia (HAP), trauma, and community-acquired pneumonia (CAP) as the cause of ARDS were observed in 21.16%, 37.05%, and 33.33%, respectively, in the study group. The incidence of HAP, trauma, and CAP was 32%, 32%, and 36%, respectively,

in the control group [Table 1]. The pre-treatment data are tabulated in Table 1 which shows no statistical significant difference between the methylprednisolone and control groups in all parameters except PEEP, protein S, Pao2 levels, and fibrinogen content. The values for these parameters were significantly higher in the methylprednisolone group when compared with the control group. The O2sat, PaO2, pCO2, HB, and creatinine were higher in the control group when compared with the methylprednisolone group before treatment [Table 1].

Post-treatment parameters after 1 week were compared with the pre-treatment parameters in both the study and control groups. It was observed that there were significant improvements of pulse, temperature, systolic blood pressure, PEEP, lactate, D-dimer, creatinine, and aspartate transaminase (AST) values in the methylprednisolone group. It was also observed that there was a significant increase of PaCO2 in the control group [Table 2].

Table 1: The demographic data, clinical data, ventilator parameters, ABG, biochemical examination, and chest X-ray in methylprednisolone group and control group on the 1st day of the study

	Study group (*n*=24)	Control group (*n*=25)	*P* value
Mean age	44.12±10.75	48.5±11.26	0.175
Gender			0.523
Male	15 (62.32%)	16 (64%)	0.612
Female	09 (37.50%)	09 (36%)	0.243
Cause			
HAP	7 (21.16%)	8 32%)	0.101
CAP	8 (33.3%)	8 (32%)	0.298
Trauma	9 (37.5%)	9 (36%)	0.382
comorbid			
0	7 (21.16%)	6 (24%)	0.231
1	8 (33.33%)	8 (32%)	0.412
2	6 (25%)	6 (24%)	0.154
3	3 (12.5%)	5 (20%)	0.613
X-ray before	3.79±1.40	3.56±2.44	0.331
pulse	102.48	110.15	0.041
Temperature	37.84	37.92	0.712
Systolic BP	122.82±13.55	123.85±2.99	0.252
Diastolic BP	71.65±4.38	69.70±4.25	0.173
FIO2	89.97±15.34	82.64±5.38	0.218
PEEP	11.68±4.11	09.39±4.60	0.043
PS	16.34±3.15	14.50±3.89	0.010
O2 SAT	98.66±6.78	97.46±3.78	0.029
PaO2	71.28±5.15	81.37±5.69	0.018
PH	7.45	7.19	0.471
INR	1.29±0.72	1.45±0.37	0.713
Lactate	3.64±0.31	2.98±05	0.512
APTT	32.67±3.80	34.15±1.80	0.711
WBCs	17.92±2.48	16.75±3.18	0.329
Hb	91.23±16.35	90.56±18.66	0.021
Platelet	176±87.18	198±64.35	0.219
D-dimer	505±102.37	476±113.60	0.548
Na	142.50±6.11	140.65±3.99	0.718
K+	3.89±0.92	3.90±0.79	0.121
Creatinine	97.59±21.09	182.30±42.69	0.037
Bilirubin	36.22±7.88	32.65±7.25	0.387
AST	47.50±27.75	232.56±178.75	0.045
ALT	75.38±28.89	104.55±69.77	0.115
GGT	93.45±8.42	196.36±131.15	0.213
Albumin	26.90±3.87	27.65±5.10	0.401
Fibrinogen	9.60±1.86	8.01±2.08	0.038
CRP	241.25±89.60	11.60.62±2.18	0.194
Protein C	101.49±11.21	110.50±19.02	0.279
Protein S	118.60±19.76	123.80±21.06	0.301

D-dimer: Degradation product of cross-linked fibrin, AST: Aspartate transaminase, ALT: Alanine aminotransferase, Protein S: Vitamin K-dependent plasma glycoprotein synthesized in the liver, Protein C: Auto prothrombin IIA and blood coagulation factor XIV. ABG: Arterial blood gase, BP: Blood pressure, PEEP: Positive end-expiratory pressure, INR: International normalized ratio, CRP: C-reactive protein

DISCUSSION

ARDS is a rapidly progressive disorder that initially manifests as dyspnea, tachypnea, and hypoxemia and later quickly evolves into respiratory failure. The AECC has published diagnostic criteria for ARDS: Acute onset; ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of 200 or less, regardless of positive end-expiratory pressure; bilateral infiltrates seen on frontal chest radiograph; and pulmonary artery wedge pressure of 18 mm Hg or less when measured or no clinical evidence of left atrial hypertension.[8] Acute lung injury (ALI) is a slightly less severe syndrome characterized by less profound hypoxemia, but otherwise similar diagnostic criteria to ARDS[9,10] by the AECC defines ARDS as: (1) Acute onset of respiratory symptoms, (2) chest radiograph with bilateral infiltrates, (3) pulmonary artery wedge pressure (PAWP) of <18 mmHg (indicating no evidence of left heart failure), and (4) ARDS: PaO2/FIO2 ratio <200 mmHg. Treatment with drugs in ARDS is limited. Although Cochrane studies mention the use of surfactant therapy useful in children, its role in adults is controversial.[11] The use of corticosteroids in the management of ARDS is controversial. Few randomized controlled trials and cohort studies support early use of corticosteroids (with dosages of methylprednisolone ranging from 1 to 120 mg per kg per day) for decreasing the number of days on a ventilator; however, no consistent mortality benefit has been shown with this therapy.[12,13] In the present study, methylprednisolone was used in a regimen described in the materials and methods for 4 weeks. In ARDS, the evolution of systemic and pulmonary inflammation in the 1st week of mechanical ventilation determines the physiologic progression (resolving vs. unresolving) and outcome of the disease.[4] Glucocorticoid treatment-induced downregulation of systemic inflammation in ARDS is associated with a significant improvement in

Table 2: The clinical data, ventilator parameters, ABG, biochemical examination, and chest X-ray in methylprednisolone group and control group after 14th day of the study

Observations	Study group (*n*=24)	Control (*n*=25)	*P*
Pulse	93.50±14.86	113.11±4.26	0.015
Temperature	37.48±0.62	37.30±0.33	0.031
Systolic BP	146.47±14.99	125.13±13.02	0.041
Diastolic BP	71.00±13.38	65.56±6.82	0.174
FIO_2	65.90±10.40	63.64±15	0.916
PEEP	8.15±1.85	10.34±1.20	0.031
RR	13.99±1.65	15.88±1.67	0.029
PS	13.78±2.01	11.43±1.91	0.624
O2 SAT	98.17±2.35	100.01±1.36	0.063
PaO_2	83.20±8.32	81.61±09.74	0.858
$PaCO_2$	26.11±14.99	47.09±5.70	0.001
PH	7.10±0.08	7.27±0.08	0.141
INR	1.17±0.11	1.29±0.31	0.074
Lactate	1.58±0.60	2.38±0.19	0.003
APTT	31.87±1.72	36.95±4.14	0.001
WBCs	12.00±1.93	12.89±1.64	0.717
HB	99.23±3.54	95.48±2.45	0.128
Platelet	242.36±99.35	185.33±439.16	0.114
D-dimer	240.39±45.47	489.61±215.09	0.004
Na	140.50±4.78	140.56±0.53	0.761
K	3.85±0.61	3.47±0.27	0.034
Creatinine	72.17±19.80	121.59±413.38	0.011
Bilirubin	22.82±10.43	25.24±4.66	0.749
AST	32.59±09.90	65.67±35.53	0.027
ALT	40.33±09.20	62.54±29.32	0.219
GGT	49.60±12.61	207.24±289.18	0.318
Albumin	24.00±1.99	27.61±2.84	0.652
Fibrinogen	6.07±1.46	7.94±1.92	0.157
CRP	106.33±75.04	138.11±49.90	0.315

BP: Blood pressure, PEEP: Positive end-expiratory pressure, INR: International normalized ratio, CRP: C-reactive protein, AST: Aspartate transaminase, ALT: Alanine aminotransferase

pulmonary and extrapulmonary organ dysfunction and a reduction in the duration of mechanical ventilation and ICU length of stay.[4] In the present study, the aim was to evaluate the effect of methylprednisolone when used early in ARDS. There was no statistical significance between the methylprednisolone and control groups in relation to demographic data, etiology of ARDS, comorbidity, chest X-ray and most of clinical parameters, ventilator parameters, and biochemical investigations. It denotes that the both groups were comparable. After the 1st week of treatment, there were significant improvements of clinical parameters (pulse, temperature, and systolic blood pressure), peep (one parameter from lung injury score), lactate, D-dimer, and AST and highly significant improvement of creatinine in the methylprednisolone group when compared to the control group. In a similar study by Meduri,[4] who studied 91 patients with severe early ARDS (<72 h), 66% with sepsis, patients were randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) versus placebo. Patients were randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) versus placebo. The duration of treatment was up to 28 days and found patients with methylprednisolone achieving the primary endpoint of a 1-point reduction in LIS. In this study after 14 days from starting the treatment, there were significant improvements of clinical parameters (pulse and systolic blood pressure), ventilator parameters (FIO2, peep, and RR), systemic inflammation markers organ functions (O2sat, lactate, creatinine, WBCs, AST, and GGT), and CRP. Moreover, there was a significant improvement of CX-ray and earlier extubation from mechanical ventilation and improvement of mortality in the methylprednisolone group when compared with the control group, improvement of mortality reflection to improvement of clinical status, oxygenation, inflammatory markers, and early extubation of this group. Moreover, there were significant decreases of protein C and protein S in the control group. This indicates worse clinical outcomes, including death, fewer ventilator-free days, and more nonpulmonary organ failures in this group.[12] Annane *et al*.[7] conducted a study with a long course of a low dose of corticosteroids in ARDS over a period of 28 days and observed a reduced all-cause mortality in Intensive Care Unit and hospital mortality and decreased incidence of infection. The findings of the study by Annane *et al*.[7] are similar to the present study with reduced mortality and improved oxygenation and parenchymal recovery of pulmonary infiltration at the end of 28 days period.

CONCLUSIONS

Including methylprednisolone in addition to regular ventilator support and treatment protocol of ARDS patients, when used on first 7 days, improves the LIS, decreases the systemic inflammation, allows earlier extubation from mechanical ventilation, and decreases the incidence of hospital-acquired infection.

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