Effect of Methylprednisolone Treatment in Patients with Early Acute Respiratory Distress Syndrome

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ABSTRACT

Objective: Despite the high incidence and poor outcomes of acute respiratory distress syndrome (ARDS), it has no specific treatment. Many pharmacological therapies have been investigated in several studies, but there are limited treatment options with proven efficacy. The aim of our present study was to determine the effect of methylprednisolone treatment on mortality and morbidity rates in early ARDS.

Methods: Forty-seven patients with ARDS who underwent mechanical ventilation (MV) between January 2008 and December 2012 were enrolled in this study. They were classified into two groups: methylprednisolone group (22 patients) and control group (25 patients). Those in the methylprednisolone group received a 2-mg/kg intravenous loading dose of methylprednisolone on the first day, followed by an infusion of 0.5 mg/kg every 6 h on days 2–15 and of 0.25 mg/kg every 6 h on days 16–22.

Results: The weaning rate from MV was significantly higher (p=0.005), duration of MV was shorter (p=0.021), and mortality rate was lower (p=0.013) in the methylprednisolone group than in the control group. In Kaplan–Meier analysis, survival probabilities in the methylprednisolone group were significantly higher than those in the control group (p=0.022). Furthermore, the lung injury score, multiple organ dysfunction syndrome score, and C-Reactive Protein levels were lower in the methylprednisolone group. However, there were no differences between the two groups in terms of the day ARDS developed, duration of ARDS, and length of stay.

Conclusion: Our study showed that early methylprednisolone treatment in patients with ARDS provides significant recovery in pulmonary and extrapulmonary organ function, increases the possibility of weaning from MV, and reduces the mortality rate.

Keywords: Acute respiratory distress syndrome, methylprednisolone, mechanical ventilation, mortality

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an acute respiratory failure syndrome that is unresponsive to oxygen therapy; it is characterized by diffuse infiltration in both lungs. ARDS is frequently encountered in intensive care units (ICUs) and has no specific treatment. It requires ventilatory support and has a high mortality rate (1-4). Alveolar and/or vascular epithelial injury has been blamed for the pathogenesis of ARDS. There is acute and intense inflammation. Despite numerous research studies related to ARDS pathogenesis and treatment (2-4), there are limited treatment options with proven efficacy (5). To control systemic inflammation, researchers have focused on various mechanical ventilation (MV) strategies and therapies.

Corticosteroids are potent anti-inflammatory and immunomodulatory drugs that show inhibitory effects at various stages of the inflammatory cascade. Therefore, they are regarded as a sensible option in the treatment of ARDS (6). While some studies have shown that steroids reduce cellular and biochemical markers of inflammation and tissue injury, thus improving pulmonary functions and survival in ARDS (7, 8), others have pointed out that corticosteroids have no role in the treatment of early or late ARDS (9, 10). However, in recent years, treatment dosage and duration have been identified as important factors to determine the efficacy of corticosteroids in ARDS treatment. It has been shown that short-term, high-dose steroid therapy is not useful (11, 12). On the contrary, low-dose (1–2 mg/kg/day) and longer term steroid therapy in ARDS has been shown to reduce systemic side effects and improve outcomes including mortality rates (8).

The aim of our present study was to investigate the effects of methylprednisolone treatment on pulmonary/extrapulmonary function and survival in early ARDS. We also determined the effect of methylprednisolone on the duration of ventilator-free days and length of stay.

This study was presented as poster presentation in 19th International Intensive Care Symposium, 10-11 May 2013, İstanbul, Turkey.

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METHODS

This comparative clinical trial complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Medeniyet University, Göztepe Training and Research Hospital (date: 24.01.2013, number: 30/D). Forty-seven patients aged between 18 and 80 years who were diagnosed with ARDS based on the 1994 "The American–European Consensus Conference Committee" criteria and who were followed up in our ICU between January 2008 and December 2012 were enrolled in the study. In all patients with ARDS, conventional MV was employed based on the PaO_2/FiO_2 ratio. As conventional treatment, positive end-expiratory pressure (PEEP) titration, prone positioning, inverse ratio ventilation, recruitment maneuvers, and high-frequency ventilation were performed. Because this study was a retrospective study, there was not informed patient consent.

In our clinic, low-dose (1–2 mg/kg/day) and long-term intravenous methylprednisolone therapy was initiated in patients with ARDS as routine therapy after 2010 because it has been shown to reduce systemic side effects and improve outcomes including mortality rates (7, 8). Thus, the patients were divided into two groups according to whether patients received this therapy. Twenty-five patients who received only the conventional treatment were included in the control group (patients before 2010), whereas 22 patients who received the methylprednisolone treatment protocol in addition to the conventional treatment were included in the methylprednisolone group (patients after 2010). The methylprednisolone treatment protocol was a 2-mg/kg intravenous loading dose (in 30 min) on the first day, followed by an infusion of 0.5 mg/kg every 6 h from day 2 to day 15 and 0.25 mg/kg every 6 h from day 16 to day 22.

Demographic data, ARDS etiology (primary/secondary), day of ARDS development on admission to the ICU, number of days with ARDS, duration of MV, length of stay in the ICU, and outcome (survival/death) were recorded for all patients included in the study. The static lung compliance and degree of infiltration present on a chest radiograph were determined by the lung injury score (LIS), which uses a 4-point score based on the PEEP level and PaO_2/FiO_2 ratio (13). After the diagnosis of ARDS, the LIS, multiple organ dysfunction syndrome (MODS) score, and serum CRP levels were recorded in each patient for 22 days. The LIS was used to evaluate pulmonary function, and the MODS score and CRP levels were used to evaluate systemic function and inflammation.

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences for Windows version 22.0 (SPSS Inc.; Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation, and categorical variables were expressed as percentage. Normality assessment of continuous variables was performed with the Kolmogorov–Smirnov and Shapiro–Wilk tests. To compare continuous variables, Student's t-test was used for parametric variables and the Mann–Whitney U test was used for non-parametric variables. The Friedman test was used for the comparison of repeated measures that did not show normal distribution. Categorical variables were compared with the chi-square and Fisher's exact tests. The Kaplan–Meier survival test was used to determine the effect of methylprednisolone on survival. $p<0.05$ was accepted as the level of statistical significance.

RESULTS

Twenty-five patients received only conventional treatment (control group), whereas 22 patients received the methylprednisolone treatment protocol in the present study. When the methylprednisolone group was compared with the control group, demographic data, ARDS etiology, and length of stay in the ICU were not significantly different. Additionally, the day of ARDS development (6.8±7.8 vs. 6.1±5.6, p=0.925) and duration of ARDS (10.2±5.1 vs. 12.3±5.3, p=0.355) were similar in the methylprednisolone and control groups. However, the methylprednisolone group had a significantly higher weaning rate (54.5% vs. 16%, p=0.005) and shorter MV duration (10.8±7 vs. 18±3.4, p=0.021) (Table 1).

Patients were compared in terms of their LIS scores after the diagnosis of ARDS. While the initial LIS scores in the methylprednisolone group were significantly higher ($p<0.05$), the methylprednisolone group had significantly lower LIS scores on days 13, 16, 19, and 21 of follow-up than the control group ($p<0.05$, for all). Additionally, when the LIS scores in both groups were compared with the initial scores, the control group did not show statistical difference through the course of follow-up while the methylprednisolone group showed a significant decrease in the LIS scores starting from day 4 ($p<0.05$) (Figure 1a).

Upon the diagnosis of ARDS, the MODS scores on days 4, 6, 8, and 10 in the methylprednisolone group were significantly lower than those in the control group ($p<0.05$, for all), whereas the scores were similar in both groups at other times post follow-up ($p>0.05$). When compared with the initial values, the changes in

Table 1. Demographic data, ICU length of stay, and ratios of weaning from MV in the control and methylprednisolone groups

	Control (n=25)	Methylprednisolone (n=22)	p
Age (years)	52.8±18.8	44.8±17.2	0.136
Weight (kg)	71.8±6.75	75.1±10.8	0.211
Gender M/F	17/8	19/3	0.138
Etiology			
Pulmonary (%)	12 (48)	14 (63.6)	
Extrapulmonary (%)	13 (52)	8 (36.4)	0.282
ICU length of stay (day)	19.7±10.7	18.8±10.7	0.435
Day of ARDS development	6.1±5.6	6.8±7.8	0.925
ARDS duration (day)	12.3±5.3	10.2±5.1	0.355
MV weaning ratio	4 (16%)	12 (54.5%)	0.005
MV duration (day)	18±3.4	10.8±7	0.021

M: male; F: female; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; MV: mechanical ventilation

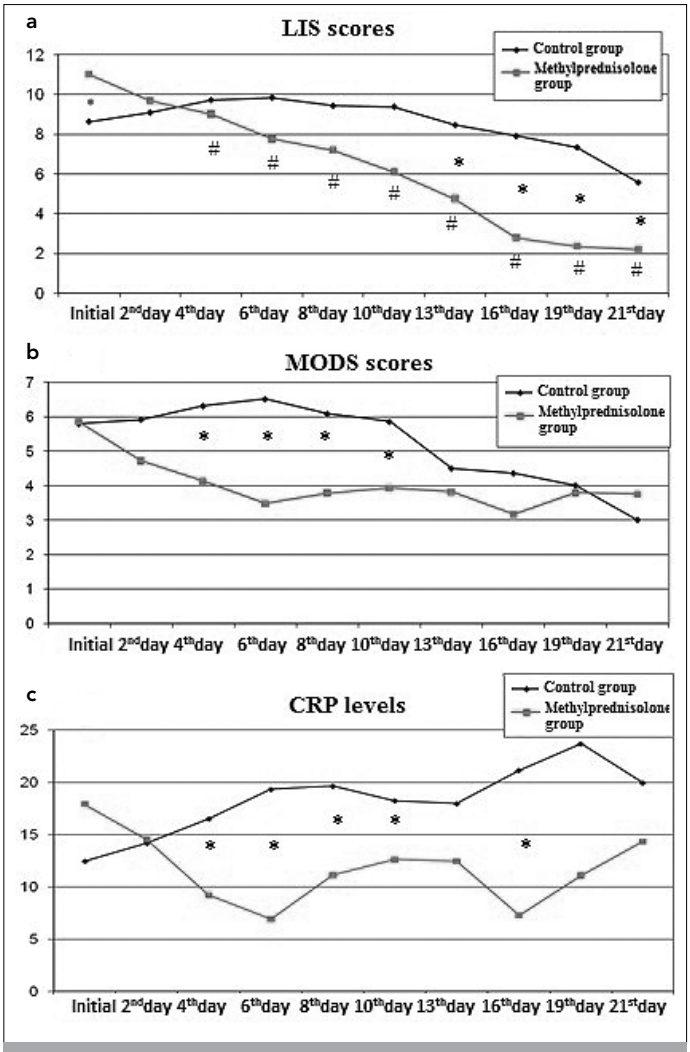

Figure 1. a-c. LIS scores of the patients (a). MODS scores of the patients (b). CRP levels of the patients (c). *p<0.05 versus control group, #p<0.05 versus the initial LIS score in the methylprednisolone group

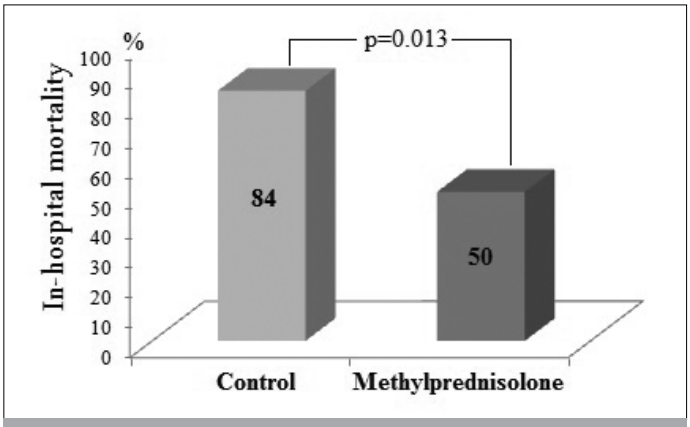

Figure 2. In-hospital mortality rates in the control and methylprednisolone groups

the MODS scores did not show any statistical difference in either group (Figure 1b). When compared in terms of CRP levels, levels on days 4, 6, 8, 10, and 16 in the methylprednisolone group were significantly lower than those in the control group (p<0.05, for all) (Figure 1c).

Table 2. Effect of methylprednisolone use on the duration of MV

	Control (n=25)	Methylprednisolone (n=22)
Day 5	0.920±0.054	0.938±0.061
Day 10	0.880±0.065	0.865±0.089
Day 15	0.494±0.104	0.793±0.107
Day 20	0.224±0.088	0.721±0.119
Median±SE	40.22±7.13	23.80±3.39
95% CI	26.23–54.20	17.15–30.44
	Log rank: 4.02	p=0.045

Table 3. Effect of methylprednisolone use on survival

	Control (n=25)	Methylprednisolone (n=22)
Day 5	0.920±0.054	0.950±0.049
Day 10	0.880±0.065	0.950±0.049
Day 15	0.553±0.101	0.785±0.096
Day 20	0.298±0.193	0.624±0.128
Median±SE	18.52±1.86	28.05±3.74
95% CI	14.89–22.26	20.73–35.37
	Log rank: 5.23	p=0.022

The effect of methylprednisolone treatment on the probability of weaning from MV was analyzed with the Kaplan–Meier test. The probabilities of weaning from MV on days 15 (79.3% vs. 49.4%) and 20 (72.1% vs. 22.4%) in the methylprednisolone group were significantly higher than those in the control group (p=0.045) (Table 2)

The in-hospital mortality rate of the study group was 68.1%. It was significantly lower in the methylprednisolone group than in the control group (50% vs. 84%, p=0.013) (Figure 2). When the effect of methylprednisolone treatment on survival was analyzed with the Kaplan–Meier test, day 15 (78.5% vs. 55.3%) and 20 (62.4% vs. 29.8%) survival probabilities in the methylprednisolone group were significantly higher than those in the control group (p=0.022) (Table 3).

DISCUSSION

The main finding of our study was that the in-hospital mortality rate was significantly lower in patients with ARDS who received methylprednisolone treatment compared with the control group. In addition, the weaning rate from MV was higher, duration of MV was shorter, and the LISs, MODS scores, and CRP levels were lower in the methylprednisolone group than in the control group.

Many studies have examined the effectiveness of corticosteroids on both preventing and treating ARDS after disease development (14-16). Some studies have shown that short-term, high-dose steroid treatment does not have beneficial effects (11, 12). A study conducted by Steinberg et al. (17) regarding the efficacy and reliability of corticosteroids in ARDS revealed that methylprednisolone administration in patients with ARDS for at least 7 days does not have a favorable effect on the mortality rate. On the contrary, methylprednisolone is associated with significantly increased 60- and 180-day mortality rates among patients enrolled at least 14 days after the onset of ARDS. Khilnani and Hadda (18) found that the administration of corticosteroid for preventive purpose in critically ill patients increased the rate of mortality and risk of ARDS development; nevertheless, they suggested that the administration of corticosteroids at the very early phase of ARDS has beneficial effects (18, 19). These data suggest that the administration of methylprednisolone in high-risk patients has no beneficial effect on the prevention of ARDS development, but rather increases ARDS development risk and mortality rate. Additionally, the initiation of steroid treatment long after the development of ARDS might have some detrimental effects. Based on these clinical data, the preventive use of corticosteroids before the development of ARDS and administration of methylprednisolone during late ARDS are not currently recommended.

One important factor for methylprednisolone efficacy in ARDS treatment is dose and duration. Animal studies have shown that prolonged corticosteroid treatment is effective in acute lung injury by reducing edema and collagen accumulation and that the early withdrawal of corticosteroids reduces these favorable effects (20, 21). In previous studies, high-dose corticosteroid treatment was administered within a maximum timeframe of 48 h (short-term, high-dose steroid treatment), which, to a certain degree, might explain why corticosteroid treatment was ineffective in those studies (22, 23). On the contrary, some other studies have shown beneficial effects of low-dose corticosteroid treatment in critically ill patients, such in those having septic shock (24). For this reason, we examined the effectiveness of low-dose, long-term methylprednisolone treatment that was initiated on the day of ARDS development.

There was no significant difference between the control group and methylprednisolone group regarding basal demographic data, the day of ARDS development, or the duration of ARDS in our study. However, we found that the methylprednisolone group had a statistically significant higher rate of weaning from MV, shorter duration of MV, and lower rate of in-hospital mortality. The first randomized clinical study to investigate the efficacy of low-dose and long-term methylprednisolone treatment in ARDS was performed by Meduri et al. (8). Similar to our study, they showed that the duration of MV and length of stay in the ICU were shorter and that the rate of mortality was lower in patients receiving methylprednisolone. When all these findings are evaluated together, it can be concluded that low-dose and long-term steroid treatment initiated in the early period after the development of ARDS improves in-hospital outcomes including mortality rates.

In our study, we used the LIS to evaluate pulmonary function and the MODS score and CRP levels to evaluate systemic function and inflammation. LISs significantly decreased 13 days after methylprednisolone treatment, while MODS scores and CRP levels significantly decreased 4 days after treatment. Additionally, in the methylprednisolone group, LISs after day 4 were significantly lower than initial LISs and the number of ventilator-free days was higher. These results suggest that methylprednisolone treatment provides significant improvement in pulmonary and extrapulmonary organ function. Similar to our study, Meduri et al. (8) reported that LISs, MODS scores, and CRP levels are significantly lower on day 7 of corticosteroid treatment in early ARDS and that the number of ventilator-free days is higher. The most important difference between that study and ours is that we found that LISs, MODS scores, and CRP levels were low even at the long-term follow-up.

Early ARDS is characterized by a potent proinflammatory response; therefore, anti-inflammatory drugs are expected to be beneficial at this stage (19). Corticosteroids have potent anti-inflammatory effects, showing inhibitory effects at various steps in the inflammation cascade (6). For this reason, low-dose and long-term methylprednisolone treatment initiated in the early period of ARDS results in favorable changes in pulmonary and extrapulmonary tissues via the inhibition of systemic inflammation. These favorable changes induced with corticosteroid treatment allow for reduced rates of mortality and increased number of ventilator-free days in these patients. In our study, methylprednisolone treatment increased the probability of the survival rate and weaning from MV. Our results were consistent with previous findings, and to the best of our knowledge, we are the first to show the positive effect of methylprednisolone treatment in a Turkish population. For this reason, physicians should keep in mind that low-dose and long-term corticosteroid treatment initiated in the early period of ARDS in the ICU might have important contributions to the prognosis.

One major limitation of our study is the inadequate number of patients in both study groups. Another limitation is the lack of long-term follow-up. Large-scale prospective, randomized clinical trials with long-term follow-up are necessary.

CONCLUSION

Acute respiratory distress syndrome is a condition in which intense inflammatory processes are triggered. Low-dose, long-term corticosteroid treatment initiated at the early period of the disease results in profound improvement in pulmonary and extrapulmonary tissues via the inhibition of systemic inflammation, increases the probability of weaning from MV, and significantly reduces the rate of mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Medeniyet University, Göztepe Training and Research Hospital.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

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Materials – T.B.T., E.N.K., H.G.Ö., E.E.; Data Collection and/or Processing – T.B.T., E.N.K., H.G.Ö., E.E.; Analysis and/or Interpretation – T.B.T., E.N.K., H.G.Ö., E.E., M.G.Ç.; Literature Search – T.B.T., E.N.K., H.G.Ö., E.E.; Writing Manuscript – T.B.T., M.G.Ç.; Critical Review – T.B.T., M.G.Ç.

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