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Effectiveness and Safety of Moderate-Dose of Hydrocortisone in Persistent Acute Respiratory Distress Syndrome: a Multicenter RC Trial

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Abstract
ARDS refers to the acute hypoxemic respiratory disease and pathological affects in the lung occurring as a result of an acute lung injury. We sought to test the safety and efficacy of moderate-dose hydrocortisone in ARDS patients with nonresolved ARDS in this multicenter, randomized, controlled trial. There were 210 patients included into the investigation, who were randomized as to hydrocortisone or placebo. The first outcome was 60-days mortality, and the secondary ones were ventilator-free days, ICU-free days, and adverse reactions like neuromyopathy. Even though hydrocortisone did not show any benefit in terms of 60 and 180 days survival, there was a significant increase in ventilator-free days and days free of ICU. It was however linked with a higher rate of neuromyopathy especially to those reintubated. The time of corticosteroids administration was also a very important factor and those patients who were administered more than 14 days after the development of ARDS showed much higher mortality rate. These results indicate that although hydrocortisone has short-term benefits in terms of cardiopulmonary status, its application in the medical condition, especially more than 14 days later, can introduce negative changes and increase fatal outcomes, which challenges its regular utilization in chronic ARDS.
Keywords: ARDS, Hydrocortisone, corticosteroids, ventilator-free days, ICU-free days, neuromyopathy, mortality.

INTRODUCTION
ARDS is due to an inflammatory phenomenon in the lungs causing the disease clinically characterised by acute hypoxemic respiratory failure (1). Pathologically, the ARDS mediates the occurrence of intricate alterations of the lungs tissues, which commence with an initial exudative, a proliferative, and fibrotic period (2,3). The presence of persistent inflammatory activity (4,5), continual process of parenchymal cell proliferation (3), and aberrant collagen deposition (3,6-8) are characteristic features of persistent ARDS and the entities may be potentially responsive to administration of corticosteroids.
The past studies involving the application of high dose of corticosteroids that are designed to last a shorter period in the ARDS treatment of the early-stage patients have shown no mark of survival (9-12). Nevertheless, a few more limited case series have demonstrated that moderate-dose corticosteroid treatment could be beneficial to patients who have persistent ARDS

(8,1317). In one of the randomized, single-center studies (24 patients with ARDS of seven days duration or longer), moderate dose corticosteroids were used to treat ARDS, resulting in improvement of both lung performance and survival (18).

The dangers of corticosteroid therapy in these patients are still unclear. Researchers in studies of sepsis and ARDS patients have indicated that administration of corticosteroids in very high doses can elevate the risks of secondary infections in the patient (11, 12, 19, 21), However meta-analysis of moderate dose corticosteroids in sepsis refused to confirm this dread (22). The other dangers of use of corticosteroids include hyperglycemia, delayed healing of wounds, psychosis, pancreatitis, and long-lasting muscle-weakening, which might worsen the functional restoration process (23).

The purpose and objectives of conducting this study was that by doing this study, we conducted a multicenter, randomized, controlled trial that was used in proving the effectiveness and safety of moderate-dose hydrocortisone on chronic ARDS patients. Our hypothesis was that the clinical outcomes of a moderate-dose of hydrocortisone administration would be improved, under the conditions of relative low risk of complications occuring.

Methods

Patients

Mandated patients who received mechanical ventilation through intubation could be enrolled between 7 and 28 days following initial presentation of ARDS as earlier described (1). Barometric pressure was corrected by adjusting the ratio of partial pressure of arterial oxygen(PaO2) against fraction of inspired oxygen (FiO2) in Denver and Salt Lake City. Permanent bilateral infiltrates and keeping on mechanical ventilation since the beginning of ARDS until the entry into the study were mandatory. The PaO2:FiO2 ratio, on the day of entrance into a study, was required to be lower than 200. Supplementary Appendix refers to exclusion criteria.

Study Protocol

By using a randomly assigned strategy of the permuted blocks method, the patients were assigned to be administered intravenous hydrocortisone sodium succinate (hydrocortisone) in a dose diluted in 50 ml of 5 percent dextrose in water or a placebo of 50 ml of 5 percent dextrose in water, stratified by hospital. One single dose of 2 mg hydrocortisone per kilogram of predicted body weight and then 0.5mg per kilogram of predicted body weight was given after every 6 hours of 14 days followed by 0.5 mg per kilogram of predicted body weight after every 12 hours 7 days after which the dose was tapered gradually. Tapering was done within a period of 4 days assuming that they completed 21 days of the treatment and the patient could not breathe on his/her own within 48 hours. In case of disseminating fungal infection or septic shock, or in the event that the patient was capable of breathing on his/her own accord within 48 hours, symptoms were tailed within 2 days.

A weaning process in the ventilator was also outlined in the protocol. Daily weaning-readiness assessment and use of pressure-support ventilation was done to wean the patients once their arterial oxygenation could satisfactorily be supported with FM02 of 0.5 or less.

The demographic data, physiological variables, radiographic findings, pre-existing conditions, and drugs were captured during entry to the study and days 1, 2, 3, 4, 5, 7, and 14, 21, and 28.

The patients were trailed until they died or were released home breathing freely without the support of a machine or attained 180 days or sooner chambered in the case.

Monitoring and Infection Surveillance

Daily monitoring of patients including monitoring of cardiovascular events; renal events; liver events; coagulation events was done in 28 days. The failure of an organ was characterized by the failure of normal performance in any manner, and a patient was able to be released when they have attained lack of failure of an organ, indeed at the time of being discharged out of the hospital premise. Blood, cerebrospinal fluid, and pleural and urine 105 and greater colonies per milliliter were recorded as positive cultures of normally sterile sites. Evidence of serious infections including nosocomial pneumonia, disseminated fungal infection or sepsis, was reviewed weekly using the chart and data on other infections were obtained. Bone marrow plasma and as described above (25) were collected at admission and 7 days and processed in the bronchoalveolar-lavage and plasma samples.

Neuromyopathy Events

In the initial stages of the study, there are 6 adverse events involving neuropathy, myopathy, or myositis associated with the patients involved in a certain treatment group. In response to data and safety monitoring board request, the charts of 88 patients who were enrolled earlier were examined regarding the presence of neuromyopathy, which was described by such terms as myopathy, myositis, neuropathy, paralysis, and unexplained weakness. These cases were reviewed by the data and safety monitoring board together with an NHLBI-designated neurologist and suggested that the study be continued. Prospective review of the charts of final 91 patients enrolled was done.

Statistical Analysis

Mortality after 60 days of enrolment was the main outcome. Patients were labeled as survivors in case they were released to go home and continue breathing without the use of a ventilator within 60 days. It was compared on the basis of the intention-to-treat. In the first study, it was estimated that 400 patients will be needed to detect a 15 percent absolute difference in mortality rates between groups receiving placebo and hydrocortisone (50 percent as compared to 35 percent mortality) at a power of 85 percent. Nevertheless, it was found that 2 years later, the number of patients participated had decreased, and consequently, the study size was changed to 210 patients giving 85 percent to achieve a study powered with a significant effect level of two-sided level of 5 percent applicable in decreasing mortality rate by 40 to 20 percent. The symmetric stopping boundaries (two-sided a=0.05) were used to conduct interim analyses when about 60 patients were enrolled.

Secondary outcomes comprised the count of ventilator-free days (the amount of days that patients survived and came back to breathing autonomously without the requirement of the ventilator) and the amount of days without the deficiency of organs in the first 28 days. Other secondary events were infectious complications, an increase in the levels of inflammation and fibroproliferation markers at day 7 and how they interacted with the treatment and specific covariates, including PaO2:FiO2 ratio, respiratory-system compliance, minute ventilation, time since the development of ARDS (greater than 13 days compared to 7-13 days), and high levels

of procollagen peptide type III at the start. Other covariates Namely tidal volume and date of enrollment were also put into analysis. The Wald test and logistic-regression were used to determine the statistical interactions, and fatality rates compared with Fisher exact test. Calculations of Wilson confidence intervals were done.

When the study was concluded it was found 52 patients were still hospitalized and 12 were still receiving the mechanical ventilation 60 days after the enrollment. In order to complete information regarding outcomes, the record of patients was followed till 180 days of enrollment. Site investigators made this review without information on the treatment assignment of patients. The trial was conducted using 210 patients because of recalculation of the required sample size taking into consideration early survival data and low patient accrual rates.

Results

In the study, we considered the baseline information on the ARDS patients, clinical, and adverse events in patients with ARDS aiming at establishing the impact of hydrocortisone treatment in placebo.

A total population of all studies constituted 210 patients where 105 patients were grouped in both the treatment groups (Table 1). The average age of patients was 48.7 16.2 years and the majority of the group belonged to men (60 %). Stratification characteristics were also similar at baseline, such as length of stay in hospital prior to entry into the study, APACHE III score and the Glasgow Coma Scale scores. Regarding lung injury, more patients [56 percent] were considered to be directly injured by the lung as compared to the 44 percent of the patients that were injured indirectly. The other baseline variables including systolic blood pressure, glucose level and score of the lung injury were found to be similar in the two groups.

The complementary results at 60 days (Table 2) indicated that there was hardly any difference between the placebo group (30.2%) and hydrocortisone group (29.5%) with insignificant result (P=1.0). Nonetheless, hydrocortisone had a pronounced effect of increasing the ventilator-free days (12.5 +/- 10.2 vs. 7.2 +/- 8.9, P<0.001) & ICU-free days (9.7 +/- 8.5 vs. 6.8 +/- 8.1, P=0.03) as opposed to placebo. In addition, the proportion of severe cases of adverse events of myopathy or neuropathy was also reduced in patients in hydrocortisone group (0 vs. 10, P=0.001), and they were less prone to pneumonia occurrence (7% vs. 15%, P=0.04). The other statistic, the reduced incidence of shock (7/6 vs. 18/16, P=0.02), was also brought about by hydrocortisone. The occurrence of serious infections did not have any significant difference (P=0.12).

Mortality rates were comparable in the two groups at 180 days (Table 3; 32.3 per cent in placebo and 31.2 per cent in hydrocortisone, P=1.0). The Ven-free days (median 160 vs. 150, P=0.04) were greater in the hydrocortisone group with fewer assisted-ventilater days (median 12 vs. 19, P=0.30). No notable disparities amid the populations in ICU-free days or aggregate days of hospitalization occurred. The incidence of neuromyopathy favoured the hydrocortisone group (28% vs. 22%, P=0.21), but with a non-significant difference. There was a huge disparity in terms of mortality that was actually contingent upon when randomization occurred with greater deaths occurring amid those who randomized over 14 days after the incidence of ARDS in the hydrocortisone stratum (48% vs. 14%, P=0.02).

All in all our results show that hydrocortisone lead to better short-term clinical outcomes such

as higher ventilator-free and ICU-free days but failed to lead to a 60 or 180-day survival benefit. In addition, it is paramount to point out that the time when corticosteroids should be used played a critical role because delayed introduction of the medication (after 14 days of the first manifestation of ARDS) was linked to higher mortality rates. Hydrocortisone decreased the occurrence of pneumonia and shock, but it was correlated with an increase in incidence of neuromyopathy, which should be put as consideration when using corticosteroids to treat persistent ARDS.

Table 1: Patient Baseline Characteristics per Randomization Time in Patients with ARDS

Characteristic	Total Population	Randomization within 7–13 Days after ARDS Onset	Randomization within 14–28 Days after ARDS Onset
Age (yr)	48.7 ± 16.2	48.3 ± 18.7	50.2 ± 17.1
Male sex (%)	60	62	58
Days in hospital before study entry (d)	13.1 ± 7.1	13.4 ± 6.9	11.8 ± 7.0
Days from ARDS onset to study entry (d)	11.7 ± 3.9	11.5 ± 4.5	9.8 ± 2.3
No. of nonpulmonary or CNS organ failures	0.7 ± 0.5	0.8 ± 0.7	0.7 ± 0.6
No. of patients	210	105	105
Category of lung injury (%)			
- Trauma	14	13	14
- Sepsis	20	16	22
-Multiple transfusions	2	2	2
- Aspiration	17	16	18
- Pneumonia	40	39	41
- Other	7	7	—
Direct lung injury (%)	56	58	64
Indirect lung injury (%)	44	42	36
No. of radiographic quadrants involved	4.0 ± 0.5	4.0 ± 0.5	4.0 ± 0.5
APACHE III score†	85.4 ± 28.7	88.4 ± 27.9	87.1 ± 30.0
Glasgow Coma score†	8.7 ± 4.2	8.3 ± 4.4	8.9 ± 4.1

Systolic blood pressure (mm Hg)	121.5 ± 23.5	120.9 ± 22.3	123.6 ± 25.0
Albumin (g/dl)	2.0 ± 0.5	2.0 ± 0.5	2.0 ± 0.5
Glucose (mg/dl)	145.2 ± 56.1	153.2 ± 70.5	148.1 ± 53.2
Bilirubin (mg/dl)	1.4 ± 2.3	1.6 ± 3.5	1.3 ± 2.2
Highest creatinine (mg/dl)	1.4 ± 1.4	1.4 ± 1.5	1.5 ± 1.5
White-cell count (per mm³)	14,259 ± 18,115	15,295 ± 8,223	13,889 ± 7,212
Hematocrit	31.3 ± 4.9	30.3 ± 5.0	32.0 ± 4.8
Arterial pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1
FiO_2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
PaO_2 (mm Hg)	72 ± 13	73 ± 12	70 ± 15
$PaCO_2$ (mm Hg)	36 ± 15	54 ± 17	52 ± 16
PaO_2/FiO_2	128 ± 41	127 ± 39	130 ± 43
Plateau pressure (cm of water)	34.2 ± 10.1	34.8 ± 10.2	33.6 ± 9.4
Cst (ml/cm H_2O)	25.1 ± 11.2	23.5 ± 10.6	24.6 ± 10.9
Lung Injury Score	3.1 ± 1.1	3.3 ± 1.0	3.0 ± 1.1
Tidal volume (ml/kg of predicted body wt)	7.5 ± 2.1	7.3 ± 2.2	7.6 ± 2.0
PEEP (cm of water)	12.5 ± 4.7	13.0 ± 5.4	12.7 ± 5.3
Total minute ventilation (liters/min)	13.0 ± 4.2	12.7 ± 4.1	13.1 ± 4.4

Table 2. Adverse Events and Clinical outcomes by 60 days of Placebo and Hydrocortisone Group

Variable	Placebo (N=105)	Hydrocortisone (N=105)	P Value
60-Day mortality (%)	30.2	29.5	1.0
95% CI	21.5–39.8	20.7–38.3	
No. of ventilator-free days at day 28	7.2 ± 8.9	12.5 ± 10.2	<0.001
No. of organ-failure–free days			
- Cardiovascular failure	18.3 ± 9.8	21.2 ± 9.0	0.03
- Coagulation abnormalities	22.3 ± 8.9	22.1 ± 8.2	0.85
- Hepatic failure	21.8 ± 10.3	21.4 ± 10.0	0.73
- Renal failure	22.0 ± 10.4	23.4 ± 8.9	0.31
No. of ICU-free days at day 28	6.8 ± 8.1	9.7 ± 8.5	0.03
No. of serious adverse events associated with myopathy or neuropathy	0	10	0.001
Suspected or probable pneumonia (%)	15	7	0.04

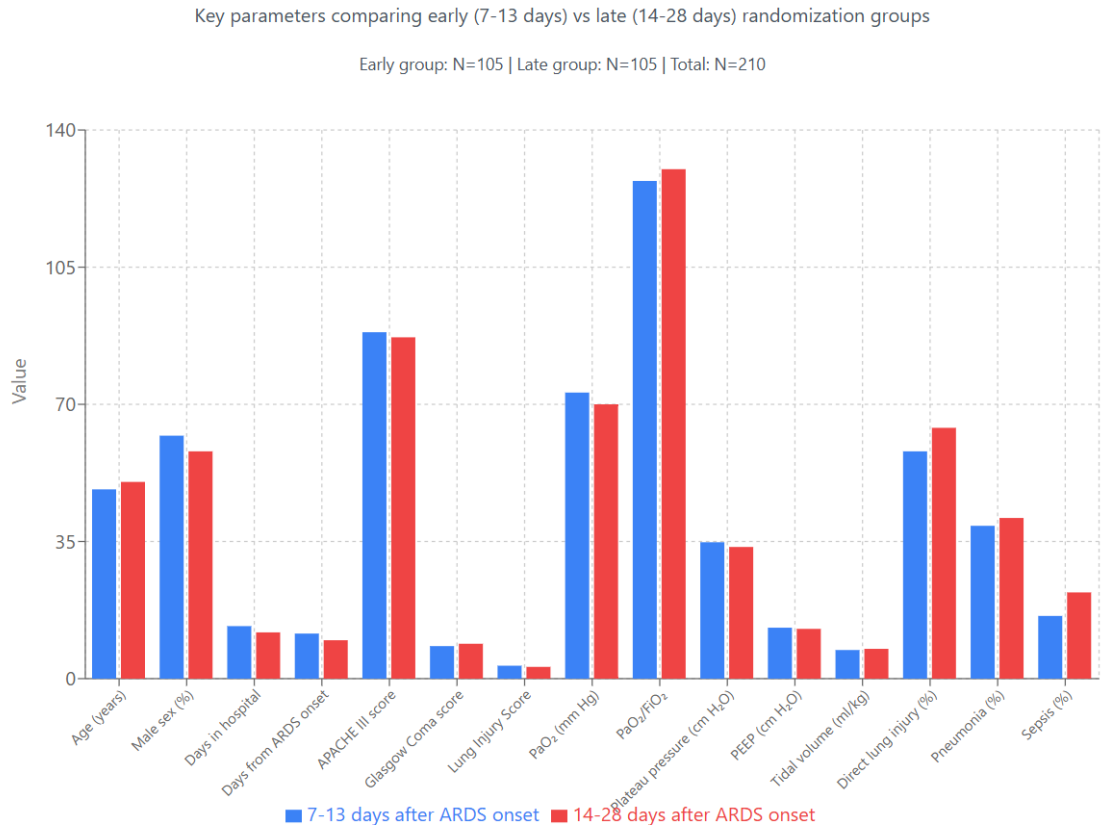
No. of episodes of shock/no. of patients	18/16	7/6	0.02
No. of serious infections/no. of patients	45/33	28/22	0.12
Amylase on day 7 (U/liter)	80 ± 55	130 ± 140	0.002
Glucose on day 7 (mg/dl)	148.5 ± 62.3	162.4 ± 66.5	0.11
60-Day mortality according to time from ARDS onset			
- 7–13 Days (%)	38	28	0.28
No. of patients	70	70	
- >14 Days (%)	32	5	0.01
No. of patients	35	35	
60-Day mortality according to baseline BAL procollagen peptide type III level			
- < Median (%)	11	39	0.02
No. of patients	25	12	
- > Median (%)	21	5	0.08
No. of patients	45	55	

Table 3. Clinical Outcomes and Neuromyopathy at 180 Days for Placebo and Hydrocortisone Groups

Variable	Placebo (N=105)	Hydrocortisone (N=105)	P Value
180-Day mortality (%)	32.3	31.2	1.0
95% CI	23.5–41.2	22.7–40.8	
No. of ventilator-free days at day 180	Median: 150	Median: 160	0.04
	Interquartile range: 0–170	Interquartile range: 12–175	
No. of ICU-free days at day 180	Median: 151	Median: 153	0.27
	Interquartile range: 0–165	Interquartile range: 12–170	
Survivors			
Days of assisted ventilation up to 180 days	Median: 19	Median: 12	0.30
	Interquartile range: 10–34	Interquartile range: 5–20	
Days of ICU stay up to 180 days	Median: 21	Median: 18	0.73
	Interquartile range: 12–32	Interquartile range: 9–31	
Days of hospitalization up to 180 days	Median: 30	Median: 27	0.73
	Interquartile range: 19–42	Interquartile range: 19–44	
Neuromyopathy — no./total no. (%)			
- Retrospective review	11/48 (23%)	16/49 (33%)	0.20

- Prospective review	12/52 (23%)	13/53 (25%)	0.75
- Overall	23/105 (22%)	29/102 (28%)	0.21
180-Day mortality according to time from ARDS onset			
- 7–13 Days (%)	40	30	0.15
No. of patients	70	70	
- >14 Days (%)	14	48	0.02
No. of patients	35	35	
180-Day mortality according to baseline BAL procollagen peptide type III level			
- ≤ Median (%)	14	42	0.03
No. of patients	26	26	
- > Median (%)	24	6	0.05
No. of patients	24	30	

Figure 1: ARDS Baseline Characteristics by Randomization Timing



DISCUSSION

Corticosteroid therapy was not useful in improving survival in the hospital as we determined in our research involving 180 patients with persistent ARDS. In addition, hydrocortisone treatment was linked with high mortality at sixth and first half a year compared with placebo treatment. Corticosteroid therapy is however seen to increase the cardiopulmonary functions in the first 3-7 days of application of the therapy and has a great effect on the progression of

ARDS. Improvement was noted in ventilator free days, ICU free-days and shock free-days in period of 28 days during and after the hydrocortisone treatment. At 180 days, the hydrocortisone group continued to incur few days that they did not require the necessity to be assisted by the ventilators compared to the placebo group. The duration of the hospital stay however did not reveal any tremendous dissimilarities in the two groups in terms of the duration that passed sometime after that. Though administration of hydrocortisone allowed patients to breathe on their own sooner than those in placebo group, the patients using hydrocortisone were more likely to require use of assisted ventilation again (28 percent in hydrocortisone group vs. 9 percent in placebo, P=0.006).

The higher rate of recurrence of assisted ventilation is likely the cause why the immediate beneficial impact of the physiological improvement in the application of hydrocortisone did not lead to the increase in survival rates. The reintubation cases experienced in the hydrocortisone group, and as a direct result, the number of patients who died (8 out of 20 patients) was more than three experienced in the placebo group (six patients). This will be as a result of problems associated with corticosteroid, side-effect that is associated with the withdrawal of corticosteroid, or pulmonary disorganizations such as redwashing of fibroproliferation that is experienced after the termination of steroid drug treatments. Though in all patients there was less occurrence of shocking effects in the group taking the drug, hydrocortisone, shock was nevertheless common among some patients who were to experience the assisted ventilation procedure again. The incidence of neuromyopathy was covered in both groups but was higher in the hydrocortisone group among the patients who required reintubation. Because the cases are not numerous, they can hardly draw definite arguments concerning the explanation of such high demand in the assisted ventilation of the hydrocortisone group.

Other studies have suggested that high dose corticosteroids expose patients with sepsis and early ARDS to secondary infection but we found out that the moderate dose of the drug that we administered did not pose the risk. We determined that a higher rate of occurrence of nosocomial infection, pneumonia, septic shock, and positive blood culture were in the placebo group. The fact that the number of people with pneumonia and septic shock was smaller in the hydrocortisone group is evidence that the problem of infections had no effect in the control group increased to assisted ventilation in hydrocortisone group.

It is not a secret that corticosteroids exert an influence on muscle activity yet it does not appear to have the same effect on the patient which is critically ill. The close relationship that existed between corticosteroid and muscle weakness in the patients that experienced assisted ventilation was also evident in the previous research findings. In spite of our cases giving us some indication of comparable rates of the clinically suspected neuromyopathy in both the groups, severe adverse events as represented by neuropathy or myopathy appeared in all the nine cases in the hydrocortisone group. This disparity should provide an indication that the administration of hydrocortisone deteriorated the level of neuromyopathy, just not the amount of the latter to the volumes which are very large. Compared cases of neuromyopathy in the two groups can be presumed to be as a result of competing: Corticosteroid-induced conduction myopathy and hyperglycemia by corticosteroid in the hydrocortisone and a long-lasting ventilation in the placebo group.

Our nerve conduction and muscle function measurement was not systematically measured and

we would have failed to detect small differences in the incidence of neuromyopathy (of the order of 25% or less). Thus, there is no information how terrible and how common neuromuscular dysfunction is in either group. Although restricted, our findings overlap with the literature and show that hydrocortisone might deteriorate clinically important neuromyopathy.

Effects of administration of corticosteroids treatment in the pre-therapeutic condition also influenced the survival of patients. The mortality of the patients who had ARDS and were subjected to hydrocortisone after 14 days was extremely high when compared to the mortality of other under-researched patients featuring ARDS and given a placebo. It is possible to assume that the patients who live longer than 14 days might possess diminished active fibroproliferation (measured by a decrease in the concentration of the peptide of procollagen type III in the lungs) and hence be less responsive to corticosteroids. The median time to treatment initiation by the reports of positive results involving the corticosteroids was similar to the time window during which patients could be enrolled in our study as well as the number of patients who were treated more than 21 days before they were enrolled in our study was low (2). There is no confirmed knowledge regarding whether and how to time the treatment of ARDS using hydrocortisone or not.

The research paper has been carried out over a duration of seven years during which the area of critical care practice has largely evolved. The interventional methods that were introduced and became prevalent included low tidal volume ventilation, rigorous control of blood glucose and corticosteroid treatment of refractory shock in septic and protocolized sedation. It is possible that such changes led to patient outcomes, but important interactions did not occur between these issues and effects of hydrocortisone on patient outcomes. Furthermore, although the levels of average glucose were more in the hydrocortisone group at various stages of the research, the level of control of glycemic may have contributed to the high level of mortality and levels of incidences of neuromyopathy.

Although the trial was not powered to detect small treatment effects, we have not performed a big effect like in the other previously done studies. The causative use of hydrocortisone augmented no infection complications, and there is potentiality that it was the cause of high incidence of neuromyopathy in the critically ill patients. Overall, our findings disapprove the necessity to use hydrocortisone as a routine examination during the progression of the long-standing ARDS and state that in case of ARDS, hydrocortisone can be harmful to initiate more than 2 weeks after the first symptoms appear.

CONCLUSION

The duration of ARDS had no impact on the study results as hydrocortisone given in moderate dose showed no difference in survival rates over 60 and 180 days despite possessing certain short-term clinical advantages, including, but not confined to, longer ventilator free and ICU free days. The point where corticosteroid is administered was another important factor so patients that were more than 14 days later after the development of ARDS had a much greater mortality rate. This implies that early use of corticosteroid can be useful and late treatment can be toxic. Moreover, it is an important fact that the use of hydrocortisone reduced the occurrence of pneumonia and shock, but increased the risk of neuromyopathy, especially among those becoming reintubated. This begs the question of the corticosteroid therapy in critically ill

patients in terms of the long-term functional effect. On the whole, the use of hydrocortisone in persistent ARDS is not supported and cannot be recommended routinely, particularly when it is initiated more than two weeks after the symptoms appeared. Although it can bring about temporary benefits in short- term cardiopulmonary ventilation, the harms it can bring, especially when exploring neuromyopathy and chances of enhanced death in case of late administration, are more than its benefits. As such, the use of corticosteroids therapy must be taken with precaution regarding time of application in treating ARDS.

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