Original Research Article

Role of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs) and hydrocortisone in COVID-19 patients admitted to the intensive care unit

ABSTRACT

OBJECTIVE:

The purpose of study was to assess the role of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and hydrocortisone in patients with COVID-19 and their outcome during hospitalization.

MATERIAL AND METHODS:

A clinical comparative prospective hospital-based study was conducted in the Department of Pulmonology & Intensive Care Unit (ICU) of Dow University of Medical & Health Sciences, Karachi in patients positive for COVID-19 infection during their hospitalization. A comparative analysis was performed between two groups, i) those who received an injection of hydrocortisone and ii) those who received oral ACEi/ARB. All the baselines and clinical variables were recorded in a structured questionnaire and the data were evaluated in the Statistical Package for the Social Sciences (SPSS) version 22.0. A p-value of <0.05 is considered statistically significant.

RESULTS:

The final analysis was performed on 130 patients among them 68 patients received an injection of hydrocortisone and 62 patients received the tablet ACEi/ARB, which ever indicated. Patients who need injection hydrocortisone were older than patients who received ACEi/ARB,

58.37±15.20 and 51.01±90.22. Patients who received injection hydrocortisone were more likely to receive mechanical ventilation support as compared to other groups, 11.7% vs. 4.8%, respectively, p-value 0.02. The overall mortality rate was 10% (n = 13) in both groups in which a higher number of deaths was observed in patients who were taking ACEi/ARB as compared to patients who were receiving injection hydrocortisone, 12.9% vs. 7.3%, respectively, but it had an insignificant association, p-value 0.17.

CONCLUSION:

We have observed in our study that patients who received an injection of hydrocortisone had lower rates of mortality irrespective of their gender and age while patients who received ACEi/ARB during hospitalization had lower complications rate but higher mortality rates.

KEY WORDS:

COVID-19, Steroids, ACEi, ARB, Death, complication, Pakistan

INTRODUCTION:

The term coronavirus is derived from the Latin word “corona” which means crown because of its similarity with solar corona under the electron microscope. Since 2002 there are three major corona viruses have been responsible for disease outbreaks and causing severe acute respiratory syndrome (SARS-CoV), followed by the Middle East Respiratory Syndrome Corona Virus (MERS–CoV) in 2012, and now the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS–CoV2). In December 2019, SARS-CoV-2 emerged in Wuhan, Hubei province of China and within a few months, the virus spread globally and in January

2020, WHO declared it as a global health emergency of international concern. On February 26th 2020 the first case of COVID-19 virus was officially declared in Pakistan since then Pakistan is dealing with the effects and side effects of the disease. To date, more than 1.2 million cases have been diagnosed in Pakistan and still cases are on the rise (1).

Both ACEi and ARBs are not only essential enzymes of the renin-angiotensin-aldosterone system (RAAS) but also beneficial for the treatment of cardiovascular-related mortality and morbidity. Previous studies on SARS-CoV have shown that the elevation of Angiotensin II contributes to the occurrence and aggravation of acute pneumonia, and that SARS-CoV infection induces a decrease in the expression of tissue ACE 2 (2). Based on these observations, researchers have advocated the use of RAAS inhibitors such as ACEI or ARBs for alleviating pneumonia injuries induced by SARS-CoV-2 (3, 4) .

The WHO Rapid Evidence Appraisal for Covid-19 Therapies (REACT) Working Group conducted a meta-analysis of seven trials that evaluated corticosteroids (mainly hydrocortisone or dexamethasone) in 1703 critically ill patients in 12 countries from 26 February to 9 June 2020, with final follow-up on 6 July. They reported in JAMA that, when compared with usual care or placebo, dexamethasone and hydrocortisone reduced the risk of death by about a third percent (5).

The evidence regarding the use of ACEi/ARB and Hydrocortisone has been observed in multiple studies but none of the studies has been conducted in our area. Secondly, a previously conducted study has shown benefits of ACEi/ARB in patients with COVID-19 were observed only in patients who had hypertension (6), which is also a limitation. That is why this study aims to

determine the benefits of hydrocortisone alone or in combination with ACEi/ARB in patients suffering from COVID-19 disease and hospitalized at tertiary care hospital, Karachi.

PATIENTS AND METHODS:

This was a clinical comparative prospective hospital-based study conducted in the Department of Pulmonology & Intensive Care Unit (ICU) of Dow University of Medical & Health Sciences, Karachi for 6 months through a convenience sampling technique.

All the adult patients (age more than 18 years) of both gender who were diagnosed with COVID-19 were enrolled in our study irrespective of their disease severity. Patients who were allergic and/or have a contraindication to Hydrocortisone and/or ACEi/ARB (Severe renal or liver impairment, and low blood pressure or shock), patients who were receiving combination therapy (injection hydrocortisone and ACEi/ARB concomitant), and patients with COVID-19 PCR positive who were isolated at home were excluded from this study.

The diagnosis of COVID-19 was made and confirmed through real-time reverse transcriptase Polymerase-Chain-Reaction (PCR) of the sample taken from nasal and/or pharyngeal swab specimens from suspected patients of COVID-19 based on their history and clinical manifestations.

A fixed-dose regimen of Hydrocortisone 100 mg every 6 hours during their hospital stay. The dose of ACEi/ARB was adjusted according to the patient's blood pressure and cardiovascular status.

A total of 130 patients with COVID-19 positive were enrolled for final analysis among 68 patients who received injection Hydrocortisone 100 mg every 6 hours alone and 62 patients received either ACEi/ARB as per recommended guidelines.

All the baseline and clinical information were gathered in a structured questionnaire. The outcome (i.e. mortality associated during hospitalization) was assessed between two groups.

DATA ANALYSIS:

Quantitative data (numerical parameters) i.e. age in years, BMI in kg/m^2, and duration of hospitalization in days was calculated as mean ± SD. Qualitative data such as gender, area of residence, marital status, current cigarette smoking, BMI categorization, comorbid, use of mechanical ventilation on admitted patients, and outcome (patients who survived or death occur during hospitalization) were calculated as numbers and percentages. Comparison of two groups (patients receiving ACEi/ARBs and Hydrocortisone) were made using independent t-test and chi-square test, where applicable. The data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0 and a p-value of <0.05 was considered to be statistically significant.

RESULTS:

The final analysis was performed on 130 patients among them 68 patients received an injection of hydrocortisone and 62 patients received tablet ACEi/ARB, which ever indicated. Patients who need injection hydrocortisone were older than patients who received ACEi/ARB, 58.37±15.20 and 51.01±9.22, respectively, (p-value 0.01). More than 80% of the patients among both groups were males. Hypertensive patients and presence of coronary artery disease in patients who received ACEi/ARB were significantly higher, 38.7% vs. 29.4% and 24.1% vs. 8.8%,

respectively, p-value 0.04 and 0.001. Patients who received Injection hydrocortisone were more likely to receive mechanical ventilation support as compared to other groups, 11.7% vs. 4.8%, respectively, p-value 0.02. Also, the mean duration of hospitalization was higher in patients who were receiving an injection of hydrocortisone as compared to other groups, 9.17±5.82 vs. 4.30±3.46, p-value 0.001. Table No. 01.

Figure No. 01 shows the outcome of patients among both groups. The overall mortality rate was 10% (n = 13) in both groups in which a higher number of deaths was observed in patients who were taking ACEi/ARB as compared to patients who were receiving injection hydrocortisone, 12.9% vs. 7.3%, respectively, but it had an insignificant association, p-value 0.17.

DISCUSSION:

Role of injectable corticosteroids particularly hydrocortisone in patients with COVID-19 PCR positive was extensively studied in multiple studies even at some stage WHO also recommended the use of corticosteroids in patients who were hospitalized due to worsening condition caused by COVID-19 infection (7). But on the other hand, data is still controversial possibly due to different variants causing different disease response and also patients' responses on different treatment strategies. The same goes for ACEi/ARBs, some studies suggest beneficial (8-10) while some studies suggest worsening effects of using these medicines in patients with COVID-19 (11, 12).

In our study we have found that patients who were receiving injection hydrocortisone were more likely to have complications like the need for mechanical ventilation support and increased duration of hospitalization as compared to patients who were receiving ACEi/ARBs. While on the other hand, higher mortality rates were observed in patients who were not receiving an

injection of hydrocortisone, but it had no significant association. A study conducted by Angus DC and colleagues (13) has shown similar findings. The beneficial effect of hydrocortisone is obvious as it prevents lung fibrosis and worsening of COVID-19 infection and ultimately prevents respiratory failure. In some studies, beneficial effects of ACEi/ARBs have been observed but they only enrolled patients with hypertension and they did not compare it with patients who were receiving hydrocortisone (14-16).

In our study we also found that patients who were receiving hydrocortisone were older, had an increased duration of hospitalization, and also needed mechanical ventilator support during their hospitalization period. This has proved that patients even after receiving mechanical ventilation had lower rates of mortality due to the beneficial effect of hydrocortisone. In our study the mortality rate among patients receiving hydrocortisone was 7.3% and among patients who received ACEi/ARB was 12.9%. A clinical trial conducted in multicenter has shown increased mortality rates (30%) even after patients were given hydrocortisone (13). Another meta-analysis conducted by Jonathan A. in collaboration with WHO has also observed higher rates of mortality (13%) in the steroids receiving group as compared to placebo (17). Their mortality rate is also higher as compared to the mortality rate observed in our study in the steroid receiving group. The two most important reasons for their higher mortality rates are the inclusion of critically ill patients and the older age population. Young patients and less underlying comorbid conditions causes less severe COVID infection and their outcome is also good (18).

Our study has certain limitations which should be considered in future studies to provide the most scientific evidence. 1) Study should be conducted on a larger scale with multicenter involvement, 2) laboratory parameters should also be included, 3) mortality should be assessed

in patients who received anti-viral therapy, other complications such as stroke, myocardial infarction, and acute kidney injury should also be observed.

CONCLUSION:

We have observed in our study that patients who received an injection of hydrocortisone had lower rates of mortality irrespective of their gender and age while patients who received ACEi/ARB during hospitalization had lower complications rates. Use of both drugs in COVID-19 patients provide benefits to the patients in terms of complications and mortality. Clinicians must consider both drugs unless contraindicated.

ETHICAL APPROVAL AND CONSENT

Ethical approval from the Institutional Review Board of the Hospital (IRB letter no: DUHS/187/20) and informed consent from the patient or accompanied attendant was taken after explaining the purpose and before the commencement of the study.

TABLE NO: 01: OVERALL BASELINE AND CLINICAL CHARACTERISTICS OF PATIENTS WITH COVID-19 RECEIVING HYDROCORTISONE AND ACEI/ARB

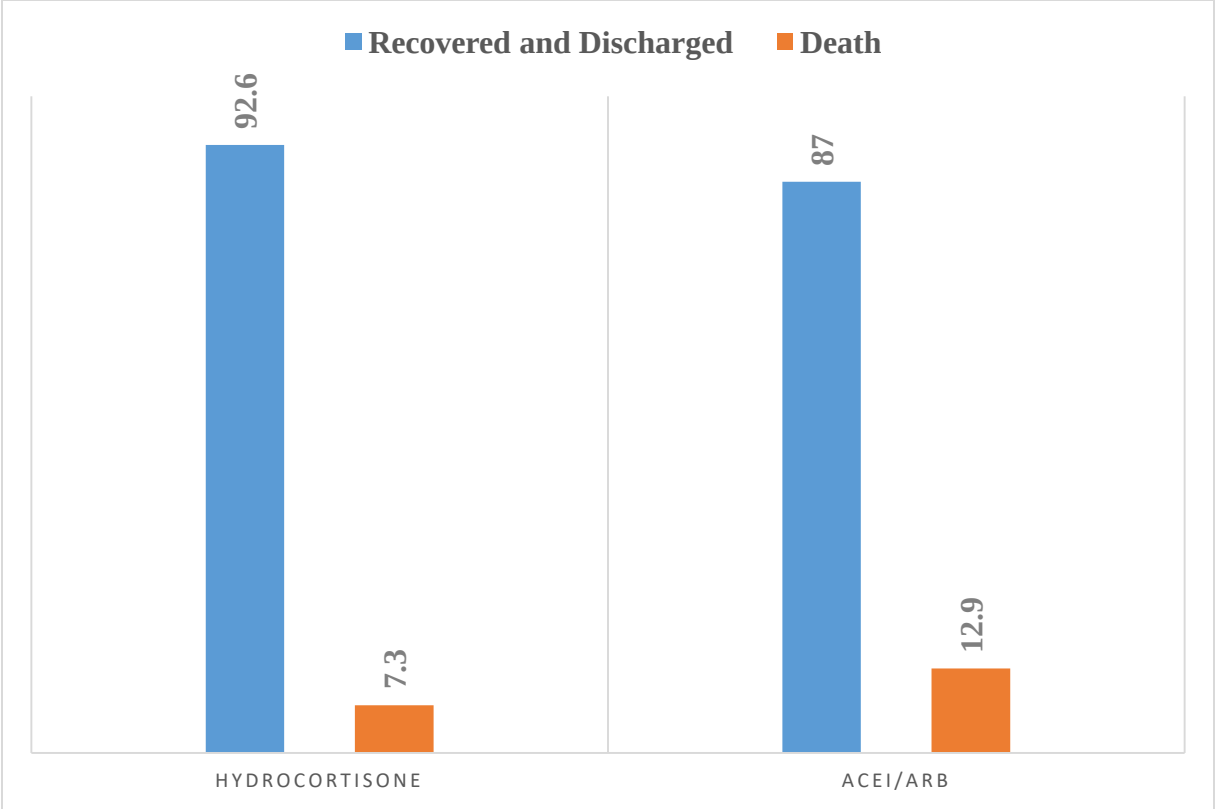
(N = 130)

Characteristics	Hydrocortisone (n = 68)	ACEi/ARB (n = 62)	p value
Age, mean±SD – Years	58.37±15.20	51.01±9.22	0.01
Gender			
Male	55 (80.8)	51 (82.2)	0.08
Female	13 (19.1)	11 (17.7)	
Area of Residence			

Urban	47 (67.1)	44 (70.9)	0.12
Rural	21 (30.8)	18 (29.0)	
Marital Status			
Single	8 (11.7)	2 (3.2)	0.27
Married	54 (79.4)	55 (88.7)	
Widow	6 (8.8)	5 (8.0)	
Cigarette Smoker	29 (42.6)	14 (22.5)	0.78
BMI - kg/m2	23.08±6.15	22.30±4.08	0.9
Underweight	2 (2.94)	4 (6.4)	0.84
Normal	40 (58.8)	47 (75.8)	
Overweight	17 25.0)	8 (12.9)	
Obese	9 (13.2)	3 (4.8)	
Comorbids			
Hypertension	20 (29.4)	24 (38.7)	0.04
Diabetes Mellitus	19 (27.9)	20 (32.2)	0.09
Coronary Artery Disease	6 (8.8)	15 (24.1)	0.001
Mechanical Ventilation			
Yes	8 (11.7)	3 (4.8)	0.02
No	60 (88.2)	3 (95.1)	
Duration of hospitalization – days	9.17±5.82	4.30±3.46	0.001

FIGURE NO. 01: OBSERVED OUTCOME IN BOTH GROUPS DURING HOSPITALIZATION

(N = 130)



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