Original Research Article

ROLE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)/ANGIOTENSIN RECEPTOR BLOCKERS (ARBS) AND HYDROCORTISONE IN PATIENTS WITH COVID-19 AND ADMITTED AT INTENSIVE CARE UNIT

ABSTRACT

OBJECTIVE:

The purpose behind this 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. Comparative analysis was performed among two groups, i) those who received injection hydrocortisone and ii) those who received oral ACEi/ARB. All baseline and clinical variables recorded in a structured questionnaire and the data were evaluated in Statistical Package for the Social Sciences (SPSS) version 22.0. A p value of <0.05 is considered to be statistically significant.

RESULTS:

Final analysis was performed on 130 patients among them 68 patients received injection 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±90.22. Patients who received Injection hydrocortisone were more likely to received mechanical ventilation support as compare to other group, 11.7% vs. 4.8%, respectively, p value 0.02. The overall mortality rate was observed 10% (n = 13) in both groups in which higher number of deaths was observed in patients who were taking ACEi/ARB as compare to patients who were receiving injection hydrocortisone, 12.9% vs. 7.3%, respectively, but it had insignificant association, p value 0.17.

CONCLUSION:

We have observed in our study that patients who received injection 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 mean crown because of its similarity with solar corona under the electron microscope. Since 2002 there are three major corona viruses 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 few months, the virus spread globally and in January 2020, WHO

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

Both ACEi and ARBs are not only essential enzymes of the renin-angiotensin-aldosterone system (RAAS) but also beneficial for the treatment for 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 RAS 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 evidences regarding use of ACEi/ARB and Hydrocortisone have been observed in multiple studies but none of the study has been conducted in our area. Secondly, 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 the period of 6 months. Ethical approval from the hospital and informed consent from the patient or accompanied attendant was taken after explaining the purpose and before commencement of the study.

All the adult patients (age more than 18 years) who were diagnosed with COVID-19 were enrolled in our study irrespective of their gender and disease severity. Patients who were allergic and/or have 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 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 for during their hospital stay. Dose of ACEi/ARB were adjusted according to the patient's blood pressure and cardiovascular status.

Comment [UL1]: Please add institutional review board because author use human as object research

A total of 130 patients with COVID-19 positive were enrolled for final analysis among 68 patients received injection Hydrocortisone 100 mg in 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) were 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, comorbids, use of mechanical ventilation on admitted patients, and outcome (patients who survived or death occur during hospitalization) were calculated as numbers and percentages. The data were entered and analysed using Statistical Package for the Social Sciences (SPSS) version 22.0 and a p value of <0.05 was considered to be statistically significant.

Comment [UL2]: Please add analysis bivariate, because author use p-value. (refer from table 01)

RESULTS:

Final analysis was performed on 130 patients among them 68 patients received injection 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±90.22, 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 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 received mechanical ventilation support as compare to other group, 11.7% vs. 4.8%,

respectively, p value 0.02. Also, mean duration of hospitalization was higher in patients who were receiving injection hydrocortisone as compare to other group, 9.17±5.82 vs. 4.30±3.46, p value 0.001. Table No. 01.

Fighure No. 01 shows outcome of patients among both groups. The overall mortality rate was observed 10% (n = 13) in both groups in which higher number of deaths was observed in patients who were taking ACEi/ARB as compare to patients who were receiving injection hydrocortisone, 12.9% vs. 7.3%, respectively, but it had 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 use of corticosteroids in patients who were hospitalized due to worsening condition caused by COVID-19 infection (7). But on the other hands, data is still controversial possibly due to different variants causing different disease response and also patient's response on different treatment strategies. 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 need for mechanical ventilation support and increased duration of hospitalization as compared to patients who were receiving ACEi/ARBs. While on the other hands, higher mortality rates were observed in patients who were not receiving injection hydrocortisone, but it had no significant association. In a study conducted by Angus DC and colleagues (13) have shown the similar findings. Beneficial effect of hydrocortisone are obvious

as it prevents from lung fibrosis and worsening of COVID-19 infection and ultimately prevents from 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 from patients who were receiving hydrocortisone (14-16).

In our study we also found that patients who were receiving hydrocortisone were older, had 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 beneficial effect of hydrocortisone. In our study the mortality rate among patients receiving hydrocortisone was 7.3% and among patients 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 steroids receiving group as compared to placebo (17). Their mortality rate is also higher as compared to mortality rate observed in our study in steroid receiving group. Two most important reasons for their higher mortality rates are 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 have certain limitations which should be considered in future studies to provide the most scientific evidence. 1) Study should be conducted on 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 injection 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.

Comment [UL3]: Please add implication practice and theoritical

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

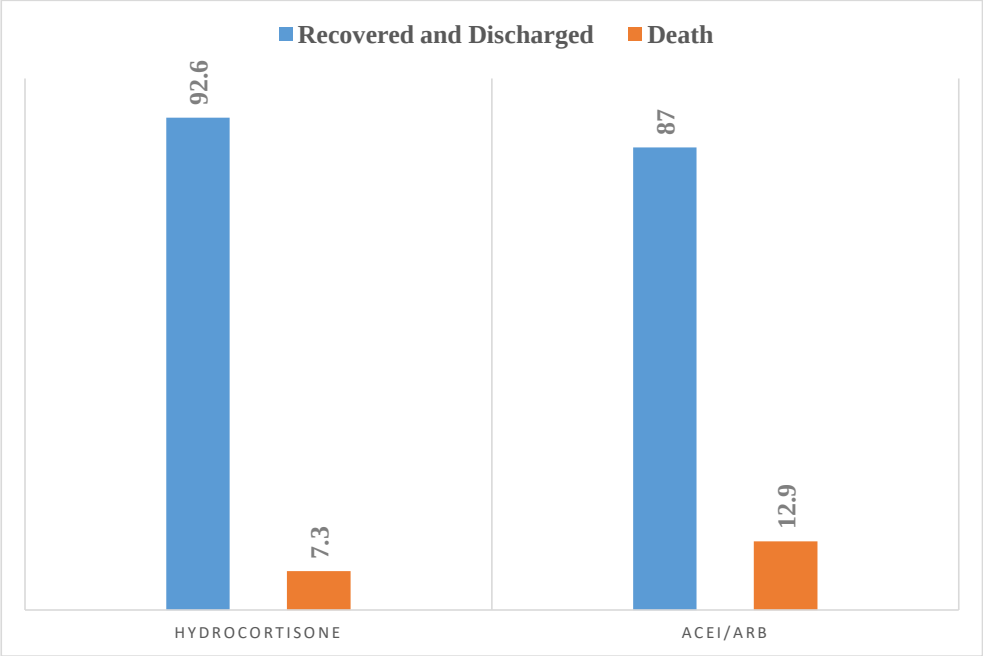
(N = 130)

Characteristics	Hydrocortisone (n = 68)	ACEi/ARB (n = 62)	p value
Age, mean±SD – Years	58.37±15.20	51.01±90.22	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)



REFERENCE LIST

1. Bhattacharyya A, Halder S, Mandal T, Sadhukhan SK, Samajdar SS, Tripathi SK, et al. Effect of Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on COVID-19 outcome: A Record Based Observational Study in West Bengal. J Assoc Physicians India. 2021;69(7):11-2.

2. Xu J, Huang C, Fan G, Liu Z, Shang L, Zhou F, et al. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in context of COVID-19 outbreak: a retrospective analysis. Front Med. 2020;14(5):601-12.

3. Wang W, Zhao X, Wei W, Fan W, Gao K, He S, et al. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) may be safe for COVID-19 patients. BMC Infect Dis. 2021;21(1):114.

4. Wang Z, Zhang D, Wang S, Jin Y, Huan J, Wu Y, et al. A Retrospective Study from 2 Centers in China on the Effects of Continued Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients with Hypertension and COVID-19. Med Sci Monit. 2020;26:e926651.

5. Group TWREAfC-TW. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-41.

6. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res. 2020;126(12):1671-81.

7. Keyt H. WHO recommends corticosteroids for patients with severe or critical COVID-19. Ann Intern Med. 2021;174(1):JC2.

8. Khera R, Clark C, Lu Y, Guo Y, Ren S, Truax B, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19. medRxiv. 2020.

9. Khera R, Clark C, Lu Y, Guo Y, Ren S, Truax B, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers With the Risk of Hospitalization and Death in Hypertensive Patients With COVID-19. J Am Heart Assoc. 2021;10(13):e018086.

10. Hakeam HA, Alsemari M, Duhailib ZA, Ghonem L, Alharbi SA, Almutairy E, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Blockers With Severity of COVID-19: A Multicenter, Prospective Study. J Cardiovasc Pharmacol Ther. 2021;26(3):244-52.

11. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112-6.

12. Wu Y. Compensation of ACE2 Function for Possible Clinical Management of 2019-nCoV-Induced Acute Lung Injury. Virol Sin. 2020;35(3):256-8.

13. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317-29.

14. Khashkhusha TR, Chan JSK, Harky A. ACE inhibitors and COVID-19: We don't know yet. J Card Surg. 2020;35(6):1172-3.

15. Limbourg FP. [Hypertension and RAAS inhibition in times of COVID-19 - current recommendations of the European Society of Hypertension.]. MMW Fortschr Med. 2020;162(9):67-9.

16. Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. JAMA Cardiol. 2020;5(7):745-7.

17. Group WHOREAfC-TW, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-41.

18. Voinsky I, Baristaite G, Gurwitz D. Effects of age and sex on recovery from COVID-19: Analysis of 5769 Israeli patients. J Infect. 2020;81(2):e102-e3.