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Original Article

Internal Medicine Section

Effect of ACEi and ARBs vs Non ACEi/ARBs in Hypertension with Respect to Renal Outcomes in COVID-19 Infection: A Retrospective Cohort Study

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ABSTRACT

Introduction: The Acute Kidney Injury (AKI) is one of the most common complications following Coronavirus Disease-2019 (COVID-19) infection. The presence of high density of Angiotensin Converting Enzyme 2 (ACE2) receptors in type 2 alveolar epithelial cells, vascular endothelium and proximal convoluted tubules explains the involvement of systemic organs in COVID-19 infection. Systemic hypertension is one of the most common co-morbidities associated with COVID-19 infection with high mortality, especially in patients of severe disease with AKI. The antihypertensives, which work by Renin Angiotensin Aldosterone System (RAAS) inhibition like ACE inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) can upregulate the enzyme ACE2, so, the incidence and risk of AKI in hypertensive patients, who have COVID-19 infection is common.

Aim: To determine the risk of developing AKI and mortality in hypertensive patients, with COVID-19 infection, on ACEi or ARBs as compared to non ACEi and non ARBs.

Materials and Methods: This was a retrospective cohort study conducted on 116 admitted hypertensive patients, who were positive for COVID-19 infection from the month of April 2021 to September 2021. The study patients were divided into two groups- group A and group B. The group A was on ACEi or ARBs and group B was on non ACEi/ARBs. The patients baseline history, clinical examination and the blood investigations like Renal Function Test (RFT), Liver Function Test (LFT), Echocardiography (ECG), Chest X-ray, 2 Dimensional-ECHO (2D-ECHO), Arterial Blood Gases (ABG) were done for all the patients. The normal Blood Pressure (BP) was less than 140/90 mmHg. The normal creatinine was 0.6 to 1.5 mg/dL and normal urea was 19 to 45 mg/dL. The RFT was repeated on every day of hospital stay duration. The patients were followed-up for one month from day of starting the study. The parameters were recorded, assessed on day 7th and day 30th, of the study. All parameters were compared between the final outcome of the patients by 30th day of study and the class of antihypertensives used to control hypertension. The Pearson's Chi-square test, Fisher's-Exact and one-way Analysis of Variance (ANOVA) were used for testing the significance of relationship and outcome between group A and group B study patients.

Results: The mean duration of hypertension in both the groups was 7.6 years. In group A 53 (45.7%) were on ACEi and ARBs, in group B, 63 (54.3%) were on non ACEi/ARBs. In the group A, the serum creatinine of more than >1.5 mg/dL at 7th day of study was found in 28 (52.8%) patients and on 30th day, it was found in 8 (15.09%) patients (p-value=0.065). Again in the group A, blood urea of more than 45 mg/dL on 7th day of study was found in 30 (56.6%) patients and on 30th day it was found in 9 (16.98%) patients (p-value=0.064). In group B, the serum creatinine >1.5 mg/dL on day 7th of study was found in 36 (57.14%) patients and on day 30th, it was in 24 (38.09%) patients (p-value=0.061). Again in group B, the blood urea of >45 mg/dL on day 7th was found in 35 (55.55%) patients and on day 30th it was found in 16 (25.39%) patients (p-value=0.074). Of the patients on group A (ACEi and ARBs) 28 (52.83%) were on supplemental oxygen, 12 (22.6%) were on Non Invasive Ventilation (NIV), one was intubated and 12 (22.6%) did not require oxygen (p-value=0.727). Of the patients on group B (non ACEi/ARBs) 33 (52.4%) were on supplemental oxygen, 12 (19.04%) were on NIV, 5 (7.93%) were intubated and 13 (20.63%) did not require oxygen. In the patients of group A, 35 (66.03%) were recovered and 18 (33.96%) died, in the group B 40 (63.49%) cases were recovered, while 23 (36.50%) died (p-value=0.781).

Conclusion: There was no significant and demonstrable association between specific groups of antihypertensives with renal outcomes and mortality in hypertensive patients with COVID-19 infection. By above observations, the present study concluded that, there is no specific role of ACE2 receptors in renal outcome and mortality in hypertension with COVID-19 infection.

Keywords: Acute kidney injury, Angiotensin receptor blockers, Renin angiotensin aldosterone system inhibitors, Systemic hypertension

INTRODUCTION

The AKI is one of the most common complications following COVID-19 infection. The extent of AKI can range from the presence of proteinuria, haematuria and can go to the level of requiring renal replacement therapy. The COVID-19-associated AKI (COVID-19 AKI) is having high mortality and acts as an independent risk factor for all-cause in-hospital mortality in patients with COVID-19 infection [1]. Systemic hypertension is one of the most common co-morbidities associated with COVID-19 infection with high mortality, especially in patients with severe disease with AKI. The presence of high density of ACE2 receptors expression in type 2 alveolar epithelial cells, vascular endothelium and proximal convoluted tubules explains, the involvement of systemic organs in COVID-19 infection. The hypertension is a major risk factor for renal and cardiovascular diseases [2]. The antihypertensives used in the age group of less than 55 years are mainly ACEi and ARBs inview of high sympathetic activity and hyper-reninaemia with hypertension. But in the age group of more than 55 years, the main

antihypertensives used are hypertension. But in Blockers (CCBs) and Thiazide diuretics [3,4]. The antihypertensives which work by RAAS inhibition like ACE inhibitors and ARBs can upregulate the enzyme ACE2, so the incidence and risk of facilitating COVID-19 infection with systemic organ injury and AKI in hypertensive patients is very common [5]. So, the present study was done to determine the risk of developing AKI and mortality in hypertensive patients with COVID-19 infection on ACEi or ARBs, as compared to non ACEi and ARBs.

MATERIALS AND METHODS

This was a retrospective cohort study conducted on 116 COVID-19 infected hypertensive patients admitted at Krishna Rajendra Hospital, Mysuru, Karnataka, India from April 2021 to September 2021.The Institutional Ethical Clearance (IEC) for the study was taken from Ethical committee, Mysore Medical College and Research Institute, Mysuru, Karnataka, India [ECREG:ECR/134/Inst/KA/2013/RR-19].

Inclusion criteria:

- Age more than 18 years.
- Hypertensive patients, who were tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by Polymerase Chain Reaction (PCR) technique.

Exclusion criteria:

- Known case of Chronic Kidney Disease (CKD).
- Derangement in kidney function at the time of admission.
- Those on nephrotoxic drugs.
- Type 2 diabetes mellitrus
- Connective tissue diseases.
- Autoimmune diseases.
- Patients on corticosteroids.
- Any other chronic drugs intake in any form.

Study Procedure

Blood pressure of more than 140/90 mmHg is considered as systemic hypertension [3,4]. The serum creatinine of 0.4 to 1.5 mg/dL and urea of 19 to 45 mg/dL was taken as the normal levels in the current study. The serum creatinine of above 1.5 mg/dL and the blood urea of above 45 mg/dL was considered to be having AKI [2,6]. The patients were divided into two groups. The group A was on ACEi or ARBs, the group B wason non ACEi/ARBs. The patients' history were recorded, clinical examination and the investigations, such as complete blood count, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), RFT, LFT, ECG, Chest X-ray, 2D-ECHO and ABG were done. The RFT was repeated on every day of the hospital stay. The patients were followed-up for one month from the day of starting the study. The parameters were recorded and assessed on day 7th and day 30th of the study. All the parameters were compared between the final outcome of the patient by 30th day of the study and the class of antihypertensives used to control hypertension. The patients' data was collected after obtaining the informed consent. The study proforma was used to collect the data of cases, such as age, gender, hypertension duration, antihypertensive medication details, co-morbidities, mode of oxygen/pressure support delivery, duration of ward/ICU stay, renal outcome and mortality.

STATISTICAL ANALYSIS

The data was analysed by using Statistical Package for the Social Sciences (SPSS) software version 22.0. The Pearson's Chi-square test, Fisher's-Exact and ANOVA was used for testing the significance of relationship between group A (ACE inhibitors and ARBs) with the group B (non ACEi/non ARBs) drugs of systemic hypertension subjects with COVID-19 infection.

The association between variables was done by using the Chi-square test. The unpaired t-test and Pearson's correlation formula was used for the assessment of qualitative and quantitative variables. The ANOVA test was used for testing the significance between the both groups. A p-value of <0.05 was considered statistically significant.

RESULTS

Total 53 (45.7%) patients were on group A (ACEi and ARBs) drugs and 63 (54.3%) on group B (non ACEi /ARBs) drugs. The mean duration of hypertension in group A was 7.1 years, and in group B, was 6.8 years. The antihypertensive drugs used in the group A patients were Enalapril in 14 (26.41%), Ramipril in 16 (30.18%), Telmisartan in 20 (37.73%) and Olmesartan in 3 (5.6%) patients. The group B patients were on Amlodipine in 36 (57.14%), Amlodipine and Hydrochlorothiazide in 21 (33.3%) and Prozosin in 6 (9.5%) patients [Table/Fig-1].

Parameters		Group A (n=53) (ACEi and ARBs)	Group B (n=63) (non ACEi/ARBs)
Mean age (years)		60	61.5
Sex	Male	28 (52.8%)	36 (57.14%)
	Female	25 (47.1%)	27 (42.85%)
Hypertension duration (years)		7.1	6.8
Mean hospital stay duration (days)		19	17.5
Mean serum CRP (mg/dL)		46.6	38
Mean SPO_2 level (%)		92.6	93.9

[Table/Fig-1]: Baseline parameters of both groups.

In both the groups, day 7th blood urea and serum creatinine were elevated as compared to the day 30th values (not significant) [Table/Fig-2].

Variables		Group A (ACEi and ARBs) in no. (%)	Group B (non ACEi/ARBs) in no. (%)
Serum creatinine (mg/dL)	>1.5 at 7th day	28 (52.8)	36 (57.14)
	>1.5 at 30th day	8 (15.09)	24 (38.09)
p-value		0.065	0.061
Blood urea (mg/dL)	>45 at 7th day	30 (56.60)	35 (55.55)
	>45 at 30th day	9 (16.98)	16 (25.39)
p-value		0.064	0.074

[Table/Fig-2]: Serum creatinine and blood urea distribution.

The association between the groups of drugs used to manage hypertension with the respiratory outcome was similar (p-value=0.727) [Table/Fig-3]. The recovery and death pattern was similar in both the groups [Table/Fig-4].

Medication details	Respiratory outcome in patients in numbers (%)				p-value
	Oxygenated in no. (%)	Nonoxygenated in no. (%)	On NIV in no. (%)	Intubated in no. (%)	
Group A (ACEi and ARBs, N=53)	28 (52.83)	12 (22.6)	12 (22.6)	1 (1.8)	0.727
Group B (Non ACEI/ ARBs, N=63)	33 (52.4)	13 (20.6)	12 (19)	5 (7.9)	
Total	61 (52.58)	25 (21.5)	24 (20.68)	6 (5.17)	

[Table/Fig-3]: Association between medications and respiratory outcomes.

Outcome in numbers (%)	Group A (ACEi and ARBs) in no. (%) out of total 53	Group B (Non ACEi/ ARBs) in no. (%) out of total 63	Total	p-value
Recovered	35 (66.03)	40 (63.49)	81 (69.8)	0.781
Death	18 (33.96)	23 (36.50)	35 (30.17)	

[Table/Fig-4]: Association between recovered and death.

DISCUSSION

The present study was done to look for the outcome with RAAS (ACEi and ARBs) inhibitors in COVID-19 infection with hypertension. In the present study, there was no significant difference in renal outcome and mortality between the drugs used to treat hypertension in COVID-19.The mechanisms postulated for the pathogenesis of AKI in COVID-19 are the direct injury to endothelium by viral tropism, induction of coagulopathy and complement activation. The indirect injury to kidney occurs through organ crosstalk, dehydration, and exposure to nephrotoxins [7-9].

The mean age of the study population was 60 years in group A and 61.5 years in group B patients, with a male preponderance of 55.2%.which was in comparison with the study by Lanzani C et al., where the average age was 67 years with 75% of male preponderance. This reflects the higher prevalence of hypertension in the elderly age group and also the higher risk of hospitalisation if they contract COVID-19 infection [10]. In the present study, the renal parameters, such as serum creatinine and blood urea were significantly elevated in both the groups in the first week of the infection. This was similar to the study by Angel-Korman A et al., [11]. AKI was common among those with COVID-19 infection and on antihypersive treatment with ACEi and ARBs. AKI was due to the elevation of ACE2 receptor with their effect on vascular endothelium [7]. The study by Khruleva Y et al., also reported that, the AKI was common in this group of patients [12].

In the present study, by the end of 30th day, the renal parameters started to come down as compared to the first week, inspite of continuing ACEi and ARBs for hypertension. This shows that the renal failure in COVID-19 infection is not completely associated with ACE2 receptors hyperfunctioning [7].

The ACE2 receptors level is higher in patients with cardiac dysfunction, hypertension, and renal abnormality on ACEi and ARBs therapy [13-15]. In the present study, the mean duration of hospital stay in both the groups was 18 days, which was similar to the study by Lanzani C et al., who reported an average hospital stay of 10 days [10]. This indicates that the COVID-19 virus infected patients would have significant systemic organs dysfunction, so such patients needs prolonged hospital admission [14,16]. In the present study, the respiratory outcomes were similar to the study by Peng M et al., where the same drugs (ACEi and ARBs or non ACEi/ARBs) were used to treat hypertension with COVID-19 infection. This shows that, there wouldn't be any association between drugs used to treat hypertension and respiratory outcomes in COVID-19 infection [17]. In the present study, the number of deaths happened between both groups were same and it was not skewed towards any specific antihypertensives group. This was in comparison with the study by An J et al., who also reported no significant correlation between the mortality and any class of drugs, used to treat hypertension in COVID-19 infection [18]. The RAAS inhibitors and all other class of antihypertensives, used to treat hypertension in COVID-19 infection for short duration, alone were not associated with poor renal outcomes [19-21]. The ACE2 receptors alone cannot be linked with any significant systemic organ dysfunction in COVID-19 infection [22-24].

Limitation(s)

This sample size was limited. The follow-up period was limited to one month.

CONCLUSION(S)

The use of any class of antihypertensive drugs (ACEi and ARBs or non ACEi/ARBs) in hypertensive patients with COVID-19 infection alone, cannot be associated with adverse renal outcomes and mortality. From the above observations, the present study suggests that, there is no specific role of ACE2 enzyme level with the renal outcomes and mortality in COVID-19 infection.

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