Original Article

Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Clinical Outcome in COVID-19 Patients with Hypertension

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Abstract

Background: Hypertension is the main factor to predict the severity and mortality of COVID-19. The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) is challenging. This study aimed to investigate the effect of ACEIs and ARBs on clinical outcomes in COVID-19 patients with hypertension.

Materials and Methods: This cross-sectional study was carried out on 498 patients who were referred to Razi hospital following COVID-19 development and also had hypertension. Patients were divided into two groups receiving drugs in the ACEIs and ARB's groups and those not receiving these drugs. The primary outcome was death up to one month after the onset of symptoms.

Results: Cardiovascular disease in patients taking ACEIs/ARBs was higher ($p<0.001$). One hundred eleven deaths (22.3%) were seen in the studied patients in whom 66 deaths (59.5%) belonged to the group not taking ACEIs and ARBs ($p>0.05$). Seventy-nine patients (15.86%) were admitted to ICU in which 62.03% of these patients died while the non-ICU mortality rate was 14.8% (Odds Ratio = 9.40; 95% CI: 5.54 to 15.95, $p <0.001$). A subgroup analysis found that among patients with diabetes who had hypertension, the incidence of death was 43.55% in the group taking ARBs/ACEi lower than in another group significant ($p = 0.021$).

Conclusion: The mortality rate in the patients taking ACEIs/ARBs is not different from other groups. It was found that among COVID-19 patients with diabetes who had hypertension, the incidence of death in the patients taking ARBs/ACEi was lower than in another group.

Keywords: COVID-19, SARS-CoV2, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, ARBs, ACEi

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Please cite this article as: Fakhrae Z, Bitaraf S, Nashibi R, Yousefi R, Ahmadi F, Khosravi S, et al. Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Clinical Outcome in COVID-19 Patients with Hypertension. J Cell Mol Anesth. 2021;6(4):323-28. DOI: https://doi.org/10.22037/jcma.v6i4.35596

Introduction

In December 2019, pneumonia was caused by a new beta-coronavirus in Wuhan, China, and on February 11, 2020, it was named COIVD-19 caused by severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The rapid transmission of SARS-COV-2 like SARS and MERS was a significant challenge in the health field worldwide (2, 3). Covid-19 is an acute respiratory disease with symptoms similar to seasonal flu and colds such as cough, headache, fever, shortness of breath (4, 5). In addition to the lungs, this virus and drugs used to treat COVID-19 can also affect other body organs, such as the liver, kidney, eye, and heart (6-8). Comorbidities such as hypertension, cardiovascular disease, and lung disease can also significantly affect the prognosis of this infectious disease (9, 10). According to studies, most patients with COVID-19 have underlying diseases such as hypertension, cardiovascular disorders, and diabetes, and the mortality rate in these people is higher than in other patients (11, 12). The cardiovascular complications following COVID-19 depend on this hypothesis that ACE2 is considered the co-receptor for SARS-CoV-2 (13). In this regard, continuing the use of ACE/ARB in COVID-19 patients is recommended based on some studies in the Korea cohort (14) and meta-analysis that reported the use of ACEI/ARB is not related to severe forms of COVID-19 or death (15). This study investigated the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on clinical outcomes in COVID-19 patients with hypertension as a cross-sectional study.

Methods

Design and setting

This cross-sectional study was carried out on 498 patients who were referred to Razi hospital following COVID-19 development and also had high blood pressure at the same time during 2020-2021. The diagnostic method for COVID-19 included clinical symptoms, chest x-ray, and Polymerase chain reaction (PCR). Also, the diagnosis of hypertension was based on the patient's self-report and antihypertensive drugs. According to a study done by Zhang et al. (16) entitled "Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19", the incidence of death following COVID-19 development in the patients with hypertension taking ARBs/ACEi was 3.7% and in the groups without taking hypertensive drugs was 9.8%, 300 patients in each group was calculated.

However, due to exit criteria and inability to complete sampling, the final analysis was done on 498 patients. Exit criterion was not taking hypertensive drugs. In this study, patients were divided into two groups who received one of the drugs in the ACEIs and ARB's groups and those who did not. The primary outcome was death up to one month after the onset of symptoms.

Data collection

Patient medical history, demographic information such as age and gender, patient's clinical characteristics such as fever, cough, fatigue and lethargy, shortness of breath, heart rate, respiration rate, and blood pressure), laboratory and radiological information, comorbidity, hospital treatment interventions and patient's clinical outcomes, duration of pre-hospital symptoms and length of stay at the hospital were collected in this study. Each patient was assigned a code. The data were double-checked to ensure the accuracy of the data.

Ethical issue

The research followed the tenets of the Declaration of Helsinki. Written informed consent was obtained, and they were free to leave the study at any time. The ethics committee approved this study of Ahwaz Jundishapur University of Medical Sciences (#IR.AJUMS.REC.1399.346).

Statistical analysis

This study presents continuous variables as a median and interquartile range, and categorical variables are presented as frequency and percentage. Logistic and Cox regression was used for univariate and multivariate analyzes. A P value less than 0.05 was considered significant in all analyses, and the tests were two-sided. The relationship between ACEIs and ARBs and death was assessed with the univariate and then multivariate approach by controlling potentially confounding variables (demographic variables, comorbidities, and clinical and laboratory symptoms). Multiple imputation method was used to solve the problem of lost data in the laboratory.

Results

This study studied 600 patients with hypertension who were referred to Razi hospital following COVID-19 development. One hundred two were excluded from the study because they did not take medication to control their blood pressure. Of the remaining patients (n=498), 240 patients took ACEIs and ARBs, and the rest took other antihypertensive drugs. The median age of patients taking ACEIs and ARBs was 64 (IQR: 56-70) years, and for another group was 68 (IQR: 58-76) years. Table 1 shows the frequency of symptoms and comorbidities between the two groups. Cardiovascular disease in patients taking ACEIs/ARBs was higher, and this difference was statistically significant (p<0.001).

One hundred eleven deaths (22.3%) were seen in the studied patients in whom 66 deaths (59.5%) belonged to the group not taking ACEIs and ARBs, and 45 deaths (40.5%) belonged to the group taking ACEIs and ARBs**.** In univariate analysis, the prevalence of death in the group taking ACEIs and ARBs was 27% lower than in another group, but this relationship was not significant (Prevalence ratio = 0.73; CI: 0.5-1.07; p=0.070). This relationship will be equal to 30% after adjusting the gender of the patients (Prevalence ratio = 0.70; CI: 0.48-1.03; p=0.073). According to table 2, 62.03% of the patients admitted to ICU died, and this ratio was 14.80% for patients not admitted to ICU. In a subgroup analysis, it was found that among patients with diabetes who had hypertension as well, the incidence of death in the group of patients taking ARBs/ACEi was 43.55% lower than another group, and this difference was statistically significant (Prevalence ratio = 56.46; 95% CI: 34.70 to 91.90, p = 0.021). At the end of the study, a power analysis was

Table 1: Demographic and clinical characteristics of the patients between the two groups.

Variable		Not taking ACEIs/ARBs	Taking ACEIs/ARBs	P value
		N=258	N=240	
Age (Median (Interquartile)		68 (58-76)	64 (56-70)	<0.001
Gender N (%)	Male	118 (45.9%)	109 (45.8%)	0.98
	Female	139 (54.1%)	129 (54.2%)	
Blood pressure Median (Interquartile)		130 (120-140)	140 (120-150)	<0.001
Fever N (%)	No	218 (87.6%)	214 (90.3%)	0.34
	Yes	31 (12.4%)	23 (9.7%)	
Cough N (%)	No	119 (46.1%)	103 (42.9%)	0.47
	Yes	139 (53.9%)	137 (57.1%)	
Headache N (%)	No	220 (85.3%)	202 (84.2%)	0.73
	Yes	38 (14.7%)	38 (15.8%)	
Diarrhea N (%)	No	246 (95.3%)	223 (92.9%)	0.25
	Yes	12 (4.7%)	17 (7.1%)	
Shortness of breath N (%)	No	99 (38.4%)	104 (43.3%)	0.26
	Yes	159 (61.6%)	136 (56.7%)	
Diabetes mellitus N (%)	No	97 (37.6%)	85 (35.4%)	0.61
	Yes	161 (62.4%)	155 (64.6%)	
Pulmonary N (%)	No	253 (98.1%)	233 (97.1%)	0.48
	Yes	5 (1.9%)	7 (2.9%)	
Renal N (%)	No	212 (82.2%)	201 (83.8%)	0.64
	Yes	46 (17.8%)	39 (16.3%)	
Cardiovascular N (%)	No	169 (65.5%)	104 (43.3%)	<0.001
	Yes	89 (34.5%)	136 (56.7%)	

Table 2: Frequency of deaths in patients taking /not taking ACEIs and ARBs, gender and hospitalization at ICU.

Group	Death	
	No	Yes
Not taking ARBs/ACEs	192 (74.42%)	66 (25.58%)
Taking ARBs/ACEs	195 (81.25%)	45 (18.75%)
Male	164 (42.49%)	63 (57.8%)
Female	222 (57.51%)	46 (42.2%)
Not hospitalized at ICU	357 (85.2%)	62 (14.80%)
Hospitalized at ICU	30 (37.97)	49 (62.03%)

Table 3: Relationship between drug type and prevalence of death by controlling the confounding variables.

Confounding variable	Prevalence ratio	Upper limit	Lower limit	P value
Age	0.805	0.549	1.181	0.267
Gender	0.704	0.479	1.034	0.073
Blood pressure at admission time	0.826	0.557	1.225	0.342
Fever on admission time	0.795	0.541	1.170	0.245
Cough at admission time	0.735	0.503	1.074	0.111
Headache at admission time	0.734	0.502	1.072	0.110
Diarrhea at admission time	0.740	0.506	1.081	0.119
Shortness of breath at admission time	0.742	0.508	1.085	0.124
Diabetes	0.732	0.501	1.070	0.107
Pulmonary	0.732	0.501	1.070	0.106
Renal	0.736	0.504	1.076	0.114
Cardiovascular	0.728	0.494	1.074	0.110

performed. The incidence of death among 240 patients in the ARBs/ACEi group and 258 patients in another group were 0.1875 and 0.2558, respectively, the absolute power was 0.41, and it is recommended to use a higher sample size for further studies. Out of 498 patients admitted to the hospital, 79 patients (15.86%) were admitted to ICU, of which 62.03% of these patients died while the non-ICU mortality rate was 14.8% (Odds ratio = 9.40; 95% CI: 5.54 to 15.95, $p<0.001$). 57.28% of the patients who were not admitted to ICU had shortness of breath, but this ratio was 69.62% in the patients admitted to ICU, and this difference was statistically significant (Odds ratio = 1.71; 95% CI: 1.02 to 2.87, $p = 0.042$).

In the multivariate analysis by controlling other variables, the prevalence of death in the group taking ACEIs/ARBs was lower than in another group, but this relationship was not significant (Table 3).

Discussion

This research was done on COVID-19 patients who had hypertension to investigate the effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on clinical outcomes in these patients with hypertension. In summary, our research showed that the mortality rate in the patients taking ACEIs/ARBs is not different from other groups, but patients with diabetes who had hypertension and the incidence of death in the patients taking ARBs/ACEi was lower than another group. A study in the United States on 12,594 hypertensive patients receiving one or more antihypertensive drugs (including two classes of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) revealed that these drugs do not affect the increased

risk and severity of CovCOVID-19 (17). Studies with smaller sample sizes in the United Kingdom and China also reported similar results (18, 19). We believe that COIVD-19 patients with hypertension had a lousy prognosis; however, the severity, clinical manifestations, and the mortality rate of COVID-19 patients in the subgroups of cardiovascular disease, diabetes, and hypertension are significantly different from other patients with coronavirus (20). High blood pressure is often associated with other risk factors such as cardiovascular disease and diabetes, which increases the risk of COVID-19, in which lack of hypertension control is independently related to increased risks of adverse outcomes following COVID-19. ARB drugs did not increase the risks of adverse events in patients with hypertension; therefore, the control and management of blood pressure in the treatment process of COVID019 patients should be considered (21).

Another study by Yang et al. showed similar results and supported using ACEIs/ARBs as antihypertensive drugs in treating COVID-19 patients (22). This study was consistent with our results because the lower mortality rate observed in the ARBs/ACEi group compared to non-ARBs/ACEi group was not significant. Our findings thus support the use of ARBs/ACE inhibitors in patients with COVID-19 and preexisting hypertension. Our subgroup study found that the incidence of death in the patients taking ARBs/ACEi was lower than in another group.

Alos, Zhou et al. showed that the use of ARBs decreases the mortality rate in COVID-19 patients, but ACEi had no effect on mortality rate (23). In the present study, we did not categorize the use of ARBs and ACEi to compare the results of Zhou et al.' study. The probable mechanism about the effect of ARBs/ACEi is the increase of the ACE2expression, which is also the cellular receptor for SARS-CoV-2 in these patients (24). According to the results, COVID-19 patients taking ARBs/ACEi have a lower risk of death than those not taking ACEis/ARBs at the time of hospitalization following COVID-19. Further studies assess ACEis/ARB's effect as a therapeutic agent in the treatment process of the COVID-19 patients as a cohort or clinical trial study.

Conclusion

The median of blood pressure and the frequency of cardiovascular diseases in patients taking ACEIs/ARBs is more. The mortality rate in the patients taking ACEIs/ARBs is not different from other groups. It was found that among COVID-19 patients with diabetes who had hypertension, the incidence of death in the patients taking ARBs/ACEi was lower than in another group.

Acknowledgment

This study was extracted from a research project encoded OG-9909. The authors would like to thank the deputy research of Ahwaz Jundishapur University of Medical Sciences.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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