Original Research Article

Is it an advantage or disadvantage to usage angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in COVID-19 patients?

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ABSTRACT

Background: The use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) is an important problem for clinicians who treat coronavirus disease (COVID-19) in patients with hypertension. The aim of the study was to reduce the confusion in this matter to some extent.
Methods: This study was carried out in the Health Sciences University, Bursa High Specialization Training and Research Hospital between 23 March to 23 June 2020. Patients were evaluated using thorax computed tomography (CT) taken during hospitalization with severity and risk scoring, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years, score >2 (CURB-65) for pneumonia.
Results: The rate of severe pneumonia was significantly higher in the group using ACEI and ARBs. CURB 65 high risk observation rate was significantly higher in the group with ACEI and ARB using. The rate of severe pneumonia observed was significantly higher in the any antihypertensive drugs using group. This risk height is more pronounced in those using ACEI and ARBs. The mortality rate of our 500 patients with COVID-19 was 2.2% (11/500). There was no history of hypertension in these 4 patients, but 1 (1/4) of these 4 patients had diabetes. Six patients were taking ACEI and/or ARB in combination with their diuretic, calcium channel blocker and beta blocker. Only one patient was taking calcium channel blocker and beta blocker.
Conclusions: The risk of severe pneumonia may increase in COVID-19 positive patients using any antihypertensive drug. It was more pronounced in those using ACEI and ARB. We believe that more comprehensive studies are needed in this about.

Keywords: COVID-19, ACEI, ARBs, Pneumonia

INTRODUCTION

ACEIs and ARBs are renin–angiotensin–aldosterone system (RAAS) inhibitors and they commonly used for treating hypertension, and heart and renal failure in the world wide. ARBs directly reduce inflammation, organ fibrosis and endothelial injury, protect mitochondrial function, maintain insulin sensitivity, energy metabolism, and lipid metabolism besides normalize the coagulation cascade. These properties of them are considered as a benefit for the patients with acute critical disorders.[1,2]

Angiotensin-converting enzyme 2 (ACE2) is involved in the pathogenesis of both hypertension and COVID-19 pneumonia. ACE2 also serves as the cellular entry point for the severe acute respiratory syndrome (SARS) virus. It is therefore a prime target for pharmacological therapy on coronavirus related diseases.[3]

SARS-CoV-2 uses ACE2 as the receptor binding domain for its spike protein (Lu et al., 2020; Wan, Shang, Graham, Baric, and Li, 2020). This leads to ACE2 downregulation, which in turn results in excessive production of angiotensin by the related enzyme. ACE, while less ACE2 is capable of converting it to the vasodilator heptapeptide angiotensin 1-7. This in turn join in to lung injury, as angiotensin-stimulated AT1R results in increased pulmonary vascular permeability and because, mediating increased lung pathology (Imai and Kuba et al).[4]

ACE2 is highly expressed in the alveolar epithelial cells in the lung, heart, kidneys, and gastrointestinal system.[5] A major beneficial property of ARBs is also reduced inflammation and endothelial and epithelial dysfunction in many organs. ARBs directly protect the lung endothelial barrier integrity of the lung disrupted by acute injury including that caused by many viruses.[2]

The use of ACEIs and ARBs is an important problem for clinicians who treat coronavirus disease (COVID-19) in patients with hypertension. It is known that mortality rate is high in the population with elderly and chronic diseases during COVID-19 pandemics. ACEIs and ARBs using rates are also high in these patients. There are conflicting publications on the usage of ACE inhibitors and ARBs in COVID-19 patients with hypertension in the literature.

In our study, we evaluated the patients who were hospitalized with the diagnosis of COVID-19 and who did or did not take ACEIs and/or ARBs by using the criteria of thorax CT and CURB-65 pneumonia severity. The purpose of our study was to shed light on this issue.

METHODS

This study was carried out in the Health Sciences University, Bursa High Specialization Training and Research Hospital between 23 March to 23 June 2020. We considered all the subjects undergoing chronic treatment with blood pressure lowering agents as hypertensives. Diagnosis of COVID-19 was made by semi-quantitative real-time reverse transcription polymerase chain reaction on nasopharyngeal swab.

Patients were evaluated using thorax CTs taken during or before hospitalization with severity and risk scoring CURB-65 for pneumonia. Criteria used in thorax CT for grading pneumonia severity: No sign of pneumonia, mild pneumonia findings: (bilateral ground glass opacities with subpleural and peripheral distribution), severe pneumonia findings: (consolidations in addition to widespread patched ground glass opacities in bilateral lobular style, peripheral location, pleural effusion, collapse or nodular bilateral opacities). Patients' history of hypertension and drug usage were investigated.

This study was approved by the ethics committee of Health Sciences University, Bursa High Specialization Training and Research Hospital. The study was conducted retrospectively by taking patient archives into consideration.

NCSS (number cruncher statistical system) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used when evaluating the study data. The suitability of the quantitative data for normal distribution was tested by Shapiro-Wilk test and graphical evaluations. Pearson chi-square test was used to compare qualitative data. Significance was evaluated at the level of $p<0.05$.

RESULTS

The study was conducted between 23 March to 23 June, with a total of 500 participants, 46.8% (n=234) female and 53.2% (n=266) male. The ages of the participants vary between 18 and 92, and the average age is 46.77 ± 15.99 years.

Table 1: Distribution of patients' demographic features.

Variables	N	Percentage (%)
Age (year)		
≤30	82	16.4
31-40	98	19.6
41-50	126	25.2
51-60	96	19.2
≥61	98	19.6
Min-max	18-92	
Median±SD	46.77±15.99	
Sex		
Female	234	46.8
Male	266	53.2
Hypertension	112	22.4
Drugs		
ACEIs	45	9.0
ARBs	33	6.6
Diuretics	30	6.0
Calcium channel blockers	34	6.8
Beta blocker	32	6.4
ACEIs and ARBs	78	15.6
Taking antihypertensive drugs	390	78.0
Not taking antihypertensive drugs	110	22.0
1 antihypertensive drug users	45	9.0
2 and/or 3 antihypertensive drugs users	65	13

Hypertension was found in 22.4% of cases (112/500). When the usage of antihypertensive drugs is analysed; there were ACEI 9%; ARB 6.6%; diuretics 6%; calcium channel blocker 6.8% and beta blocker 6.4%. But the patients generally were taking ACEI and/or ARB in combination with their diuretic, calcium channel blocker and beta blocker. Although two patients had hypertension, they were not taking any medication.

While ACEI and or ARB use was detected in 15.6% of cases (78/112); any antihypertensive medication taken in 22% of cases. There are 78% of patients who do not use any antihypertensive drugs (288/500) (Table 1).

When pneumonia status in thorax CT was examined; as it was not detected in 23.4% of cases; mild was detected in 50.4% and mild pneumonia in 26.2%.

Table 2: Thorax CT and CURB 65 results.

Variables	N	Percentage (%)
Thorax CT		
No pneumonia	117	23.4
Mild pneumonia	252	50.4
Severe pneumonia	131	26.2
CURB 65		
Low risk	455	91.0
High risk	45	9.0

According to CURB 65, 91% of cases are in low risk, while 9% are in high risk group (Table 2).

According to ACEI and ARBs usage, when pneumonia classifications in thorax CT were examined, there was a statistically significant difference between groups (p=0.001; p<0.01). The rate of severe pneumonia was significantly higher in the group using ACEIs and ARBs.

When the risks of CURB 65 were analysed according to ACEIs and ARBs usage, a statistically significant difference was found between groups (p=0.001; p<0.01). High risk observation rate was significantly higher in the group with ACEI and ARB using. ODDS value was found to be 7.603 (95% CI: 3.974-14.549) (Table 3).

According to any antihypertensive drug use, when the classification of pneumonia in thorax CT was examined, a statistically significant difference was found between the group who was taken blood pressure medication and the antihypertensive drug non using group (p=0.001; p<0.01). The rate of severe pneumonia observed was significantly higher in the antihypertensive drugs users' group.

When the risks criterion of CURB 65 were examined according to the usage of any antihypertensive drug, a statistically significant difference was found between the group who was taken antihypertensive drug and the antihypertensive drug non user group (p=0.001; p<0.01). In the group with using blood pressure medication, the high risk observed rate was significantly high. ODDS value was determined as 6.044 (95% CI: 3.196-44.430) (Table 4).

Table 3: Evaluations according to ACEI and ARBs usage.

Variables	Non using ACE or ARB (n=422)	Using ACE or ARB (n=78)	P value
Age (year)			
Median ± SD	44.25±15.30	60.42±12.38	[b]0.001**
Thorax CT			
No pneumonia	109 (25.8)	8 (10.3)	
Mild pneumonia	217 (51.4)	35 (44.9)	[a]0.001**
Severe pneumonia	96 (22.7)	35 (44.9)	
CURB 65			
Low risk	400 (94.8)	55 (70.5)	[a]0.001**
High risk	22 (5.2)	23 (29.5)	

[a] Pearson chi square test, [b] Students t test **p<0,01.

Table 4: Evaluations according to the use of any blood pressure medication.

Variables	Non using antihypertensive drugs (n=390)	Using antihypertensive drugs (n=110)	P value
Age (year)	43.16±14.98	59.59±12.54	[b]0.001**
Thorax CT			
No pneumonia	103 (26.4)	14 (12.7)	
Mild pneumonia	199 (51.0)	53 (48.2)	[b]0.001**
Severe pneumonia	88 (22.6)	43 (39.1)	
CURB 65			
Low risk	371 (95.1)	84 (76.4)	[a]0.001**
High risk	19 (4.9)	26 (23.6)	

[a] Pearson chi-square test, [b] Students t test, **p<0.01.

Table 5: Evaluations according to ACE and ARB use in the group under 65 years old.

Variables	Non using ACE or ARB (n=385)	Using ACE or ARB (n=50)	P value
Age (year)	≥65		
Thorax CT			
No pneumonia	106 (27.5)	7 (14.0)	
Mild pneumonia	199 (51.7)	24 (48.0)	[a]0.011*
Severe pneumonia	80 (20.8)	19 (38.0)	
CURB 65			
Low risk	379 (98.4)	47 (94.0)	[c]0.073
High risk	6 (1.6)	3 (6.0)	

[a] Pearson chi-square test, [c] Fisher's exact test, *p<0.05

The patients' ages were significantly higher group that were taken any blood pressure medication. The mean age of 78 patients using ACEI and ARBs was 60.42±12.38. The ages of these 50 patients were ≤65. In other words, according to the world health organization (WHO) definition, they were in the young group. Although there was widespread severe pneumonia in thorax CT in all patients under 65 and over 65, there was no significant increase in the severity of pneumonia compared to CURB 65 between them. This may be due to optional discrimination of age, one of the CURB 65 criteria (Table 5).

DISCUSSION

The role of ACEIs and ARBs in the setting of the coronavirus disease 2019 (COVID-19) pandemic is very debated issues. There have been recommendations to discontinue these medications, while, in the lacking of clinical evidence, but some researchers supported their continued usage. Since patients treated with ACEIs and ARBs will have increased numbers of ACE2 receptors in their lungs. Because of coronavirus S proteins to bind to, they may be at increased risk of severe disease outcomes due to SARS-CoV-2 infections.

Our study is a single-center retrospective study including all consecutive hypertensive subjects who presented to the COVID-19 clinics with acute respiratory symptoms/fever, and were diagnosed with COVID-19 infection between 23 March to 23 June.

Felice et al data suggests that chronic use of RAAS inhibitors does not negative correlate with an adverse clinical course in hypertensive patients.[6] Our findings contrast with the Felice et al findings. However, the number of patients in studies is close to each other (112 and 133). 112 of our patients had hypertension (112/500). Two of them were not using blood pressure medication. The patients of 40 (30%) were using ACEIs, and 42 (32%) ARBs, and 51 (38%) other antihypertensive drugs in Felice et al study. In our study using antihypertensive drugs rate were respectively ACEIs 45/110 (40.1%) ARBs 33/110 (30%). 78/110 (29.1%) of our patients were using combined antihypertensive drugs or antihypertensive drugs except ACEIs and ARBs.

There are publications supporting that there is no relationship between COVID-19 disease severity or mortality and ACEIs or ARBs use in the literature.[7,8] In our study, a negative relationship was found between disease severity and antihypertensive drug usage. In Li et al study; epidemiologic, clinical characterization, radiologic, laboratory, treatment, and clinical outcomes data were collected and analysed.[7] In our study; patients were evaluated using thorax CTs taken during or before hospitalization with severity and risk scoring CURB-65 for pneumonia. Patients' history of hypertension and using drug were investigated retrospectively. In Mancia et al study, the use of ACEIs and ARBs was more frequent among patients with COVID-19 in the Lombardy region of Italy.[8] Nevertheless, there was no evidence that ACEIs or ARBs affected the risk of COVID-19 in this study.[8] Our study supports that using ACEIs or ARBs affects COVID-19 severity.

The mean age of all patients using antihypertensive medication, including those using ACEIs and/or ARBs, was high. The ages of 50 (64%) of these patients who were taking ACEIs and ARBs was under 65. However, there was evidence of severe pneumonia in thorax CTs. We based our study on objective criteria such as radiological imaging and CURB 65. We scanned the electronic archive records of the patients. Six (6/78) of the patients taking ACEIs and/or ARB died. These patients were elderly and people with chronic diseases. However, comorbid diseases, which are likely to occur in the elderly, were outside our study. This may seem like a limit for our study, but we think it will not change the result. However, we think that more comprehensive studies are needed.

In study of Mehta et al, it was emphasized that there was no relationship between ACEIs and ARBs use and COVID-19 test positivity.[9] In Reynolds et al study, it was no difference for test positivity and disease severity between patients taking different antihypertensive drugs.[10] Patients with positive COVID-19 test were included and they were analysed according to using

pneumonia severity criteria (CURB 65 and imaging of radiology) in our study.

In some publications, it has been reported that discontinuing the drug does not prevent the severe course of the disease, apart from not increasing the risk. De Abajo et al conducted a population-based scan and analysed patients hospitalized with COVID-19 and who used RAAS inhibitors unlike our study. Our study; included patients who were hospitalized with the diagnosis of COVID-19 and who used or did not use ACEIs and ARBs.[11]

The results of Guan et al study demonstrated that patients with COVID-19 infections, and most likely treated with ACEIs or ARBs, suffered more severe disease outcomes included i.e. Intensive Care Unit (ICU) admission, mechanical ventilation, and death.[12] In our study; the patients' ages were significantly higher than the ones who have taken any blood pressure medication. The mean age of 78 patients using ACEI and ARBs was 60.42±12.38. The ages of these 50 patients were ≤65. In other words, according to the WHO definition, they were in the young group. Although there was widespread severe pneumonia in thorax CT in all patients under 65 and over 65, there was no significant increase in the severity of pneumonia compared to CURB 65 between them. This may be due to optional discrimination of age, one of the CURB 65 criteria.

The mortality rate of our 500 patients with COVID-19 was 2.2% (11/500). The average age of these 11 patients was 71.3. There was no history of hypertension in these 4 patients, but 1 (1/4) of these 4 patients had diabetes. Six of the remaining 7 patients were taking ACEI and/or ARB in combination with their diuretic, calcium channel blocker and beta blocker. Only one patient was taking calcium channel blocker and beta blocker together. In these 7 patients, hypertension was accompanied with chronic diseases such as diabetes, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney failure and congestive heart failure.

CONCLUSION

The mean age of all patients taking antihypertensive medication, including those using ACEI and/or ARBs, was high. The age of 50 (64%) of these patients taking ACEI and ARBs were under 65. However, there was an evidence of severe pneumonia in thorax CTs. We based our study on objective criteria such as radiological imaging and CURB 65. We scanned the electronic archive records of the patients. Six (6/78) of the patients taking ACEI and/or ARB died. These patients were elderly and people with chronic diseases. However, comorbid diseases, which are likely to occur in the elderly, were outside our study. This may seem like a limit for our study, but we think, it will not change the result. However, we think that more comprehensive studies are needed.

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