

The effect of ACE inhibitors on inflammation and clinical end-points in COVID-19 patients

Relationship of ACE inhibitors to COVID-19 patients

Arzu Gunturk¹, Abidin Yusuf Kavurmaci², Yasar Kucukardali², Fatma Ferda Kartufan³, Adnan Ezici², Aynur Eren Topkaya⁴¹ Department of Internal Medicine, Istanbul Florence Nightingale Hospital² Department of Internal Medicine, Faculty of Medicine, Yeditepe University³ Department of Anesthesia and Reanimation, Medistanbul Hospital, Istanbul⁴ Department of Microbiology, Faculty of Medicine, Yeditepe University, Istanbul, Turkey

Abstract

Aim: COVID-19 infection has affected the whole world. It has been speculated that the virus might hold on to angiotensin-converting enzyme 2 (ACE 2) surfaces of type 2 alveolar cells. ACE inhibitors and angiotensin receptor antagonists (ARBs) are essential antihypertensive and cardiac failure drugs in the guidelines. In this study, we aimed to find the effect of these drugs on clinical, laboratory courses, and outcomes of COVID-19 patients.

Material and Methods: We included 109 patients in this study. There were 43 patients in the ACE/ARB group and 66 patients in the non-ACE/ARB group. The mean age was 60 years in the ACE/ARB group and 52 years old in the non-ACE/ARB group. Basal symptoms, hemogram, CRP, D-dimer, LDH, Ferritin, AST, duration of hospitalization, percentage of intensive care unit (ICU) need, length of stay in ICU were compared between the groups.

Results: The mean age in the ACE/ARB group was higher than in the other group and was statistically significant ($p=.027$). The initial symptoms were not different. There were no differences between the laboratory results of the groups. The ICU need was higher in the patients who do not use the drug than in the users ($p<.020$).

Discussion: ACE/ARB usage in COVID-19 patients did not worsen the course of the disease. However, ACE/ARB users before COVID-19 pandemic were taken to ICU at a low rate.

Keywords

COVID-19, Antihypertensives, Angiotensin-Converting Enzyme 2, Angiotensin Receptor Antagonists, Intensive care

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Corresponding Author: Arzu Gunturk, İzzetpaşa Mah, Abide-i Hürriyet Cd, No: 166, 34381, Şişli, İstanbul, Turkey.

E-mail: mdarzugunturk@gmail.com P: +90 532 366 97 66

Corresponding Author ORCID ID: <https://orcid.org/0000-0002-1941-8699>

Introduction

Coronavirus-19 infection is a pandemic since February 11, 2019. The mechanisms of the infection have not been elucidated [1]. COVID-19 has spikes and binds to the cell surfaces with these spikes. The respiratory surface is especially sensitive to the virus binding. The COVID-19 virus has a 10–20 times higher affinity to ACE-2 receptors than SARS-CoV in the 2003 outbreak [2]. ACE-2 is expressed in coronary and renal vessels and epithelium of the renal tubules [3]. ACE catalyzes the conversion of angiotensin I, to angiotensin II. ACE behaves as a kininase and inhibits bradykinin [4]. Angiotensin II increases vascular resistance and produces vasoconstriction. It also maintains sodium reabsorption and induces the secretion of aldosterone. Angiotensin II is mediated by binding to two specific angiotensin II receptors: type 1 (AT1R) receptor and type 2 (AT2R) receptor [5]. Its effects are seen by AT2R. ARBs inhibit the binding of angiotensin II to AT1R [3]. ACE 2 is a homolog to ACE. ACE 2 cleaves an amino acid from angiotensin II, forming angiotensin [1-7], which regulates a pathway that has opposing physiology to ACE and angiotensin II [6]. This enzyme opposes the pro-inflammatory, pro-oxidative, vasoconstrictive, and fibrotic properties of angiotensin II [7].

Evidence shows that older adults with SARS-CoV-2 infections and cardiovascular diseases, including hypertension, are at risk of developing severe cases [8]. Some studies showed that COVID-19 patients with hypertension account for 20–30% of all patients and increase to 58.3% in the intensive care unit ([ICU]). The Renin-angiotensin system plays a vital role in hypertension and COVID-19 [9].

In this study, it was aimed to investigate whether there is a difference in laboratory values, length of hospital stay, duration of ICU stay between COVID-19 patients using ACE/ARB or not.

Material and Methods

This current study was conducted on COVID patients who were inpatient on March 15, 2020 to May 30, 2020 in Yeditepe University Hospital. Ethical approval for this retrospective, single center clinical trial (number: 1388) was provided by the Yeditepe Clinical Trials Ethical Committee, Istanbul, Turkey (Chairperson Prof. T. Çelik) on 17/02/2021. The study was conducted in accordance with the Declaration of Helsinki.

This study included 109 COVID-19 patients admitted to the hospital. There was no distinction in terms of the gender. Male and female patients were taken without any distinction. The age range was 18–85 years. The inclusion criteria were the presence of COVID-19 diagnosis, Biochemical, Serological and Radiological tests, and hospitalization for more than 72 hours. Exclusion criteria were exceptions to the mentioned age range and lack of patient approval of the study protocol.

The study groups were ACE/ARB drug users for six months before hospitalized and those who did not use these medications for at least six months. The distribution of symptom frequency, age and gender range, hospitalization and length of stay in the ICU, first and last laboratory values, follow-up of these values, and treatment options were compared. The laboratory values that we checked in our patients included Hemoglobin (Hb), Leucocytes (WBC), Neutrophile, Lymphocytes, Thrombocytes (PLT), CRP, Neutrophile/Lymphocyte Ratio (NLR), Ferritin,

D-dimer, AST, LDH, BUN, Creatinin, glucose, oxygen saturation. PCR method for COVID-19: Nasopharyngeal swabs were collected from each patient. Viral transfer tubes (vNAT, Bioeksen, Turkey) were employed to transfer the samples.

SARS CoV-2 Double Gene RT-PCR kit (Bioeksen, Turkey) was used for RNA amplification on the LightCycler 480plate-based RT-PCR instrument (Roche, Switzerland). The SARS-CoV-2 double gene RT-PCR kit targets the SARS-CoV-2 specific N (Nucleocapsid) and Orf1abgene regions. The human RNaseP gene is targeted for sample, nucleic acid extraction, and inhibition control. The shape of the growth curves was examined, and the non-sigmoidal curves were recorded as “negative”. Sigmoidal curves with cycle threshold (Ct) <38 were evaluated as “positive”. The Ct values of all positive results were recorded.

Statistical Analysis

We retrospectively examined 110 COVID-19 patients. In our study, for statistical calculations, the SPSS program was used. Initial symptoms and laboratory tests of patients, laboratory values during the clinical course and discharge period, length of hospital stay, and duration of intensive care were compared in diabetic and non-diabetic COVID patients. Demographic data, average values and percentages were used in the evaluation. A categorical Chi-square test was used in data analysis. For parametric data, Student’s T-test was used, Mann-Whitney U test was used for non-parametric data. For comparison, we were examining the course of laboratory data over time. General Linear Model Repeated Measures test was used. Non-Spearman’s Rho test when looking at the correlation of parametric values used.

Results

One hundred and nine patients were included in the study. There were 43 patients in the ACE/ARB group, and 66 patients in the other group, which did not use ACE/ARB drugs. The average age in the ACE/ARB group was 60 years, and 52 years in the non-ACE/ARB group (p=.027) (Table 1).

Table 1. Epidemiologic features, initial laboratory findings, with and without ACE/ARB

	ACE/ARB + N: 43	ACE/ARB - N: 66	P
Average Age	60.12 (17.19)	52.52 (17.44)	.027
Length of hospitalization	5.6 (5.5)	6.2 (4.8)	.573
Length of ICU stay	6.0 (3.0)	12.0 (13.0)	.454
Number of patients admitted to ICU	3 (7%)	16 (24%)	.020
Oxygen saturation	94.4 (3.4)	95.5 (2.9)	.109
CRP	49.05 (64.15)	64.87 (81.98)	.287
Leukocytes	6439 (2985)	8717 (16270)	.437
Lymphocyte	1431 (653)	2912 (12374)	.931
Neutrophils	4581 (2789)	4861 (2839)	.487
NLR	4.2 (4.8)	4.5 (4.9)	.747
Platelets	229441 (82884)	233606 (85000)	.800
Hemoglobin	12.7 (1.9)	12.7 (1.8)	.855
Ferritin	343 (1538)	979 (157)	.560
LDH	235.5 (60.2)	457.7 (110.7)	.405
AST	30.6 (14.7)	62.8 (143.8)	.135
D-dimer	1.7 (2.2)	1.6 (3.2)	.589

Table 2. Distribution of initial symptoms in patients with and without ACE/ARB

	ACE/ARB + n: 43 (n/%)	ACE/ARB - n: 66 (n/%)	P
Fever	25	48	.113
Cough	22	37	.616
Dispnea	16	19	.357
Fatigue	15	24	.375
Muscle pain	6	10	.372
Headache	3	3	.328
Nausea	4	7	.821
Diarhea	3	7	.521

Chi-square

Table 3. Anti-COVID-19 drugs and ACE/ARB drug use

	Favipiravir	Plaquenil	Kaletra	Steroid	Actemra	Vitamin D	Vitamin C
ACE/ARB(+)	10 (23.3%)	40 (93%)	8 (18.6%)	3 (7%)	2 (4.7%)	7 (16.3%)	27 (62.8%)
ACE/ARB(-)	22 (33.3%)	59 (89.4)	16 (24.2%)	7 (10.6%)	4 (6.1%)	15 (22.7%)	57 (86.4%)
p	.259	.521	.488	.521	.753	.412	.004*

*p<.05 is significant

The initial symptoms of the disease were frequent in the non-ACE/ARB group. But none of them was statistically significant (Table 2).

Duration of hospitalization, duration of ICU, oxygen saturation, CRP, leukocyte, lymphocyte, neutrophils, NLR, platelets, hemoglobin, LDH, AST, D-dimer did not have a statistically significant difference. The percentage of ICU stays was higher in patients not using ACE/ARB (24% vs. 7%) (p=.020). Use of anti-COVID-19 drugs in ACE/ARB users is presented in Table 3.

Discussion

After ACE-2 was found to be important for SARS-COV-2 infection, ACE/ARB therapies were interrogated and caused confusion and fear [10]. Some doctors discontinued these medications and prescribed other antihypertensives. It was also emphasized that "ACE-2 levels could be increased by the use of ACEIs" [11, 12]. Their contention was the upregulation of ACE-2 levels. But there was also no clear evidence for this notion. Some studies defended that ACE/ARBs had a protective effect against ARDS, lung fibrosis, asthma, and chronic obstructive lung disease in animal models [13]. In fact, the upregulation of the ACE-2 is protective for the myocardium [14]. In view of such information, we studied these issues in our hospitalized patients. We compared initial symptoms, laboratory findings, number of patients to be taken to ICU, ICU duration, oxygen saturations with or without ACE/ARB. Initial symptoms besides headache were frequent in ACE/ARB (-) group. Headache was similar in both groups. But these results were not statistically significant. There is the first case-control study that followed the inflammatory status and clinical outcome [15]. In this study, it was detected that ACE/ARB group antihypertensives were superior to other group antihypertensives in reducing highly sensitive CRP and procalcitonin levels. In our study, we compared only CRP levels. But we could not find a statistically significant difference between the groups (p=.287). In the non-ACE/ARB group, the level was slightly higher, but not

statistically significant. In our study, the number of patients who needed to be taken to ICU was less in the ACE/ARB group and was statistically significant (p= .020). Clinical outcomes and laboratory findings in our study are similar to the study by Yang et al. [15]. Clinical outcomes were not statistically significant in their study, too. Hypertension has been observed as the leading comorbidity of COVID-19 infection [16]. ACE/ARBs block the renin-angiotensin system and upregulate the ACE-2. SARS-COV-2 binds with 10-20-fold higher affinity to the ACE-2 receptor. However, this notion may change according to different races, ages, and sexes. We have some limitations in this study. This study was done with the first outbreak patients. Plaquenil was the first choice in this outbreak. Favipiravir was preferred for extremely sick patients. In our study, this medication was used more frequently in non-ACE/ARB patients. But it was not statistically significant. The sample size may be increased. Bias may exist. Mortality could not be evaluated because of the sample size.

Conclusion

In this study, the number of patients admitted to the ICU was high among non-ACE/ARB patients and was found to be statistically significant. There were no significant differences in other issues.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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