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Research Paper

Inhibition of Renin-angiotensin System and Clinical Outcomes of COVID-19

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ABSTRACT

Background and Aim: COVID-19 is an acute respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A few studies with conflicting results have been performed to evaluate the relationship between the use of angiotensin system inhibitors and COVID-19 outcomes. Therefore, this study was performed to compare the clinical and paraclinical characteristics of patients with COVID-19 in two groups of patients treated with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) and the control group (no history of ACEIs/ARBs) in Kamkar and Shahid Beheshti hospitals in Qom City, Iran from March 14, 2019, to the end of September 21, 2020.

Materials and Methods: This retrospective descriptive study was performed by reviewing the medical record of 359 patients with COVID-19, which was confirmed by a physician via lung scan or reverse transcription polymerase chain reaction (RT-PCR). We used the independent t test to compare quantitative variables and the Chi-square test to analyze qualitative variables.

Results: The common clinical symptoms, number of hospitalization days, oxygen saturation, and lung involvement were not significantly different between the two groups. Weakness, nausea, and sweating were significantly reduced in the control group compared to the ACEIs/ARBs group ($P<0.05$). Regarding the biochemical study, the patients' hemoglobin levels and lymphocyte count on the first day of hospitalization in the ACEIs/ARBs group were significantly lower than the control ($P<0.05$)

Conclusion: These findings do not provide evidence of adverse or beneficial effects of angiotensin system inhibitors, so we require more detailed studies with a larger sample size.

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in December 2019 in Wuhan, China. This viral disease spread rapidly worldwide and was recognized as a pandemic on March 21, 2020 [1]. SARS-CoV-2 is a positive single-stranded ribonucleic acid (RNA) virus that has infected many people worldwide [2]. The number of patients and deaths caused by this infection is increasing rapidly, making this disease a global concern. In Iran, the first report confirming the COVID-19 infection was published on February 19, 2020, in Qom City, Iran [3]. Currently, no effective treatment method has been found for treating COVID-19, and scientists are still trying to find new drugs with appropriate anti-viral effectiveness [4]. Recently, two combinations of molnupiravir and Paxlovid™ have been proposed as effective treatment options for COVID-19 [5]. Current findings suggest that the most common comorbidities in patients with COVID-19 infection are cardiovascular disease, hypertension, and diabetes, which can increase the risk of COVID-19-related mortality [6, 7].

Angiotensin-converting enzyme (ACE) is part of the renin-angiotensin-aldosterone system and converts angiotensin I to angiotensin II (Ang II) that possesses vasoconstrictive, inflammatory, and peroxidative effects by binding and activating Ang II receptor type I [8-10]. ACE has a homolog, ACE2, which regulates ACE function [11-13]. ACE2 is mostly bound to cell membranes and rarely exists in soluble form in circulation. The crucial and beneficial function of membrane-bound and soluble ACE2 is to break down Ang II into angiotensin-(1-9), which is then converted to angiotensin-(1-7) by a non-ACE enzyme. Also, this enzyme can directly convert Ang II to angiotensin-(1-7). Finally, angiotensin-(1-7) shows vasodilatory, anti-inflammatory, and anti-fibrotic effects by binding to mitochondrial assembly receptors. Also, ACE2 breaks down the active metabolite of bradykinin (des-Arg^9-bradykinin). By stimulating B1 receptors, bradykinin makes lung tissue endothelial cells prone to angioedema [14].

SARS-CoV-2 enters the target cells by binding to ACE2, which is expressed in different body parts, including the lungs, intestines, kidneys, heart, and blood vessels [15-17]. Studies have shown that the SARS-CoV-2 virus reduces the regulation of ACE2 and decreases its function, which can lead to bradykinin storm (low blood pressure-inflammation-pulmonary edema-myalgia-ischemia) [18].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are high blood pressure medications. These drugs reduce blood pressure by inhibiting the renin-angiotensin system (RAS) [19, 20]. Recent research has shown that the use of ACEIs and ARBs may increase the expression of the ACE2 receptor in mice, and these results have raised concerns that patients using these medications are more susceptible to COVID-19 and may be more affected than people who do not use these medications [21-23]. On the other hand, it has also been hypothesized that increasing the number of ACE2 receptors can improve outcomes in patients with acute lung injury caused by adult respiratory distress syndrome with SARS-CoV-2 infection [24]. Also, some evidence shows that stopping these drugs worsens the condition of patients infected with SARS-CoV-2, and physicians believe these drugs should be continued [25].

According to the limited and contradictory information and some hypotheses, the dangerous role of ACEIs in patients with COVID-19 has been proposed [26], and other studies have mentioned RAS inhibitors as a suitable treatment in COVID patients [27]. In this study, the relationship between the use of ACEIs and ARBs with the incidence of symptoms in patients with COVID-19 was examined.

2. Materials and Methods

This cross-sectional study was descriptive and analytical and carried out from March 24, 2019, to September 31, 2020. The study was approved by the Ethics Committee of Qom University of Medical Sciences under the ethical code: IR.MUQ.REC.1399.008. The statistical population was patients diagnosed with COVID-19 hospitalized in Kamkar and Shahid Beheshti hospitals during 1998-1999. The minimum required sample size was 288 people due to the lack of a similar study in the scientific database and considering the 25% share of cardiovascular and diabetes patients in death cases of COVID-19, the first type error equal to 5% as well as the accuracy of the study equal to d=0.05. Sampling was performed by convenience sampling from patients admitted to Kamkar and Shahid Beheshti hospitals. The inclusion criterion was the patients with COVID-19 based on clinical and paraclinical findings, lung scan, and reverse transcription polymerase chain reaction RT-PCR. The exclusion criteria included lack of information in the files, history of cancer, and immunodeficiency. A total of 550 cases were reviewed, and according to the inclusion and exclusion criteria, the information on 359 cases was recorded. The data collection checklist was completed using the patients' files and included demographic variables, clinical findings, laboratory findings,

history of medications, underlying disease history, and clinical outcomes. The data extracted from the files were compared in two groups of patients receiving drugs effective on the angiotensin system (ACEI/ARBs) and the control group who did not receive drugs. The data were analyzed using SPSS software version 25. Mean±SD was used to describe quantitative variables and frequency and percentage for qualitative data. We used the independent t-test was used to analyze quantitative data, and the Chi-square test to compare qualitative variables. The significance level in this study was considered to be 5%.

3. Results

The current study was conducted on 359 patients referred to Kamkar and Shahid Beheshti hospitals in Qom City. The Mean±SD ages of patients in the ACEI/ARBs group and control group were 14.29±64.22 and 56.05±16.53 years, with significant difference (P<0.001). The ACEI/ARBs group included 76 female patients (52.77%), and the control group included 87 female patients (40.46%), which showed a significant difference (P=0.022). The mean duration of hospitalization in the control group was 5.62±3.51 days, and in the ACEI/ARBs group, 6.08±3.95 days; no significant difference was observed (P=0.249). The breathing rate on the first day of hospitalization in the ACEI/ARBs group was significantly higher than the control group (P=0.01). Systolic blood pressure on the first and last day of hospitalization, as well as diastolic blood pressure on the first day of hospitalization, was significantly higher in the ACEI/ARBs group than in the control group. No signifi-

Table 1. Comparing demographic variables, vital signs, and clinical findings in patients with COVID-19 in different study groups

Variables		Mean±SD/ No. (%)		P
		ACEI/ARB Group n=144	Control Group n=215	
Age (y)		64.22±14.29	56.05±16.53	0.000*
Gender	Male	76(52.7)	87(40.5)	0.022*
	Female	68(47.3)	128(59.5)	
Duration of hospitalization (d)		6.08±3.95	5.62±3.51	0.249
Heart rate (the 1st day of hospitalization)		90.36±16.93	88.27±14.43	0.210
Heart rate (the last day of hospitalization)		83.10±12.09	81.71±10.91	0.279
Respiratory rate (the 1st day of hospitalization)		19.72±2.54	19.07±2.39	0.010*
Respiratory rate (the last day of hospitalization)		19.03±1.67	19.30±3.68	0.420
Systolic blood pressure (the 1st day of hospitalization)		128.8±0.49	122.23±16.31	0.003*
Systolic blood pressure (the last day of hospitalization)		122.30±16.35	116.67±13.61	0.000*
Diastolic blood pressure (the 1st day of hospitalization)		79.42±16.30	75.87±10.06	0.011*
Diastolic blood pressure (the last day of hospitalization)		75.48±9.12	73.62±10.74	0.070
Underlying disease	Diabetes	54(37.50)	53(24.65)	0.009*
	Heart disease	34(23.61)	30(13.95)	0.019*
	Kidney disease	28(19.44)	17(7.90)	0.001*
	Liver disease	14(9.72)	14(6.51)	0.266
	Pulmonary disease	24(17.36)	23(10.69)	0.069
	Anemia	2(1.38)	4(1.86)	0.733

*P<0.05 is considered as the statistical significance level.

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Abbreviations: ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blockers.

Table 2. Comparing laboratory findings in patients with COVID-19 in different study groups

Variables	Mean±SD/ No. (%)		P
	ACEI/ARB Group n=144	Control Group n=215	
Leukocyte count (×10^9/L) (the 1st day of hospitalization)	7.42±3.65	7.12±5.27	0.546
Leukocyte count (×10^9/L) (the last day of hospitalization)	10.30±1.08	9.35±1.16	0.432
Lymphocyte count (×10^9/L) (the 1st day of hospitalization)	1.39±0.19	1.77±0.75	0.000*
Lymphocyte count (×10^9/L) (the last day of hospitalization)	2.08±0.26	2.01±0.42	0.393
Platelet count (×10^9/L) (the 1st day of hospitalization)	217.22±71.94	202.20±84.33	0.072
Platelet count (×10^9/L) (the last day of hospitalization)	251.79±92.51	256.90±195.70	0.740
Hemoglobin (mg/dL) (the 1st day of hospitalization)	12.89±1.88	13.56±2.01	0.001*
Hemoglobin (mg/dL) (the last day of hospitalization)	12.13±1.85	12.84±1.97	0.770
CRP (mg/dL) (the 1st day of hospitalization)	41.44±20.61	39.08±20.09	0.284
CRP (mg/dL) (the last day of hospitalization)	13.04±5.20	13.08±5.54	0.980
ESR (mm/h) (the 1st day of hospitalization)	59.17±313.26	57.63±31.82	0.650
ESR (mm/h) (the last day of hospitalization)	64.50±10.84	38.00±17.06	0.370
LDH (U/L) (the 1st day of hospitalization)	621.14±205.03	588.47±258.99	0.185
LDH (U/L) (the last day of hospitalization)	724.77±309.50	729.90±472.07	0.820
Cr (mg/dL) (the 1st day of hospitalization)	1.20±0.50	1.21±0.65	0.881
Cr (mg/dL) (the last day of hospitalization)	1.20±0.55	1.19±0.69	0.710
Saturated oxygen percentage (the 1st day of hospitalization)	88.38±6.24	89.55±7.04	0.106
Saturated oxygen percentage (the last day of hospitalization)	91.78±5.27	91.49±6.34	0.631
CT scan (lung involvement)	103(71.52)	156(72.55)	0.831

*P less than 0.05 is considered as the statistical significance level.

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CT, computerized tomography.

cant difference was observed in heart rate between the two groups (P<0.05) (Table 1).

Studies showed that in the ACEI/ARB group, the history of diabetes (P=0.009), heart (P=0.019), and kidney (P=0.001) diseases were more than the control group and a significant difference exists between the two groups (Table 1).

Regarding the laboratory tests, a significant difference was observed in hemoglobin levels on the first day of hospitalization between the control group (13.56±2.01) and the ARB/ACEI user group (12.89±1.88) (P=0.001). Also, a significant difference was observed in the mean number of lymphocytes on the first day of hospitalization between the control group (1771.92±755.80) and the ARB/ACEI user group (198.89±1392.35) (P=0.001). No significant difference was observed in other biochemical factors either on the first day of hospitalization or on the day of discharge between the control group and ARB/ACEI (Table 2). Based on the findings in Table 2, the oxygen saturation of the patients and lung involvement were not significantly different between the two studied groups

The most common symptom observed in patients was shortness of breath (50.69% in the control group and 56.94% in the ACEI/ARBs group), and the fewest symp-

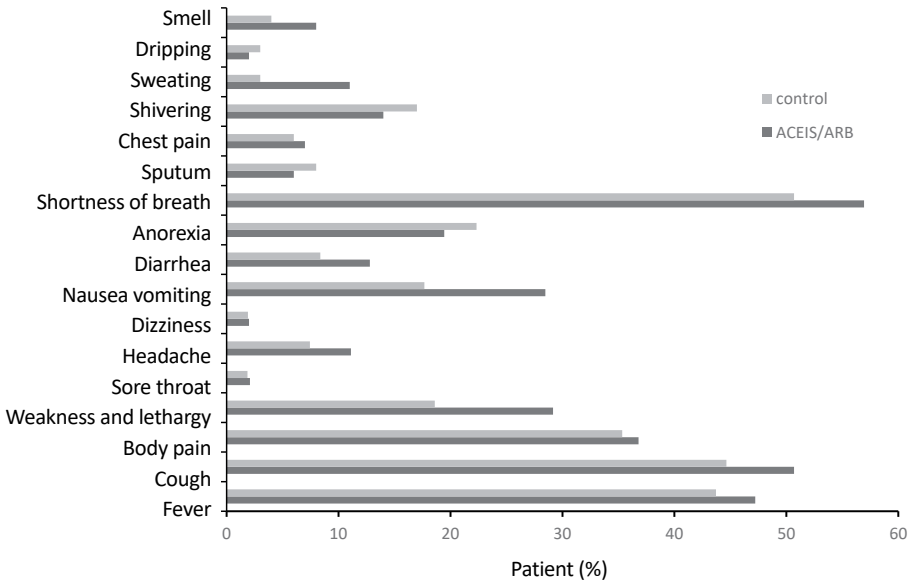

Figure 1. Clinical symptoms observed in patients with COVID-19 in the study groups

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toms were runny nose (1.39% in the control group and 1.38% in the ACEI/ARBs group), dizziness (1.86% in the control group and 2.08% in the ACEI/ARBs group), and sore throat (1.86% in the control group and 2.08% in the ACEI/ARBs group). Symptoms of fever-chills, cough, sputum, anorexia, chest pain, myalgia, reduced sense of smell, headache, and diarrhea were reported in the two groups of patients, and the Chi-square test did not show this difference to be significant (P>0.05) (Figure 1). Among the reported symptoms, the amount of weakness, lethargy, nausea, and sweating in the control group was significantly reduced compared to the ACEIs/ARBs group (P<0.05).

4. Discussion

Based on studies conducted in animal models, ACEI/ARBs increase the expression of ACE2. So, these drugs can theoretically increase the entry of the virus into the cell. On the other hand, they show anti-inflammatory effects by increasing angiotensin-(1-7) and -(1-9), which reduces lung damage [28].

Our study showed no clear association between increased risk of COVID-19 or complications associated with using ACEI/ARBs. Although some symptoms, such as systolic blood pressure and breathing rate, and some biochemical factors, such as hemoglobin level and the number of lymphocytes, were different between the two groups on the first day of the visit, the percentage of oxygen saturation, severity of shortness of breath and length of hospitalization were not statistically different. Therefore, according to this study, our findings confirm the recent recommendations of the clinical community to continue using ACEI/ARBs in patients with COVID-19. However, due to the previously stated mechanisms in some studies, an increased risk may exist [29]. Similar studies have been conducted to assess the risk of COVID-19 among ACEI/ARB users in Italy, Spain, England, and the United States of America, and the results showed that the use of ACEI/ARBs is not associated with an increased risk of COVID-19 [30-33]. A study by Lee et al. showed that the severity of COVID-19, including ICU admission, use of mechanical ventilation, and death was not greater in patients treated with RAS blockers than in controls [34]. The study by Rizk et al. also showed that ACEI/ARB in patients with COVID-19 is not associated with increased mortality and other worse outcomes [35]. Nevertheless, in another study, Abajo et al. clearly showed that compared to other antihypertensive drugs, non-use is associated with a significant reduction in the risk of hospitalization for patients with COVID-19 [33]. In addition, one study has reported an increased risk of hospitalization with COVID-19 and admission to the intensive care unit in connection with the use of ACEI/ARBs [25]. However, other observational studies have not reported using ACEI/ARBs and the risk of COVID-related complications. In a study conducted on 1128 hypertensive patients, the risk of death was lower in 188 patients using ACEI inhibitors/ARBs [23]. In a larger study conducted on 8910 patients (770 cases using ACEIs and 556 cases using ARBs), ACEIs were associated with reduced mortality in hospitals [36]. Another study also showed that the use of ACEIs/ARBs was as-

sociated with a decrease in IL6 and an increase in a cluster of differentiation (CD)3/CD8 T cells in the blood of patients with COVID-19 compared to other antihypertensive drugs [37]. Contrary to the results of these studies, in our study, no statistically significant difference was observed between the outcomes of COVID-19 in users of this drug category and those who did not use it. Therefore, it is recommended to conduct a similar study in a larger statistical population and to examine more closely all the factors related to COVID-19 in patients taking drugs that affect the angiotensin system.

5. Conclusion

Although some clinical symptoms, such as sweating, nausea, vomiting, and weakness, were less in the control group, the laboratory parameters, such as lymphocyte count and hemoglobin level on the first day of hospitalization in the treated group, were significantly reduced compared to the control group. No evidence of increased or decreased risk associated with using both classes of drugs was found in patients with COVID-19.

Ethical Considerations

Compliance with ethical guidelines

this study was approved by the Ethics Committee of Qom University of Medical Sciences with the ethical code IR.MUQ.REC.1399.008.

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Authors' contributions

Conceptualization, Methodology: Samira Khani; Data collection: Rasool Karimi Matloub and Saeed Karimi Matloub; Draft writing: Hamid Reza Ghadimi; Editing and finalization: Javad Khodadadi, Javad Tafaroji and Samira Khani.

Conflict of interest

The authors declared no conflict of interest.

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