

Impact of antihypertensive agents on clinical course and in-hospital mortality: analysis of 169 hypertensive patients hospitalized for COVID-19

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SUMMARY

OBJECTIVE: *Coronavirus disease 2019 (COVID-19) is an emerging health threat caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Previous studies have noted hypertension is associated with increased mortality due to COVID-19; however, it is not clear whether the increased risk is due to hypertension itself or antihypertensive agents. We aimed to evaluate the impact of antihypertensive agents on the clinical outcomes of hypertensive patients with COVID-19.*

METHODS: *Our study included 169 consecutive hypertensive patients hospitalized due to COVID-19 between March 20 and April 10, 2020. The demographic characteristics, clinical data, and type of antihypertensive agents being used were reviewed.*

RESULTS: *The mean age of patients was 65.8±11.7 years. 30 patients (17.7%) died during hospitalization. A total of 142 patients (84%) were using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), 91 (53.8%) were using diuretics, 69 (40.8%) were using calcium channel blockers (CCBs), 66 (39.1%) were using beta-blockers, 12 (7.1%) were using alpha-blockers, and 5 (2.9%) were using mineralocorticoid receptor antagonists (MRAs). There was no significant difference between survivors and non-survivors based on the type of antihypertensive agents being used. Binary logistic regression analysis showed that the type of the antihypertensive agent being used had no effect on mortality [OR=0.527 (0.130–2.138), p=0.370 for ACEIs/ARBs; OR=0.731 (0.296–1.808), p=0.498 for CCBs; OR=0.673 (0.254–1.782), p=0.425 for diuretics; OR=1.846 (0.688–4.950), p=0.223 for beta-blockers; OR=0.389 (0.089–1.695), p=0.208 for alpha-blockers; and OR=1.372 (0.107–17.639), p=0.808 for MRAs].*

CONCLUSION: *The type of antihypertensive agent being used had no effect on the clinical course and mortality in hypertensive patients with COVID-19. The use of these agents should be maintained for the treatment of hypertension during hospitalization.*

KEYWORDS: *Coronavirus Infections. Antihypertensive Agents. Hypertension. Hospital Mortality.*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging health threat caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Previous studies have noted that hypertension is associated with an increased risk of mortality due to COVID-19; however, it is not clear whether the increased risk is due to hypertension itself or the antihypertensive agents being used¹. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are the most important and widely used antihypertensive agents, they act by inhibiting the renin-angiotensin-aldosterone system (RAAS). It is known that coronavirus binds to the angiotensin-converting enzyme-2 (ACE-2) receptor, and there are controversial results in terms of the effects of ACEIs on the course of the disease²⁻⁴. However, the effect of other types of antihypertensive agents on this disease has not been elucidated yet. In our study, we aimed to investigate the association of antihypertensive agents and clinical outcomes of patients with hypertension and COVID-19.

METHODS

Our present study included 169 consecutive patients with a history of hypertension whose laboratory results confirmed COVID-19 and who were hospitalized in the Sakarya Education and Research Hospital between March 20 and April 10, 2020. All patients were diagnosed with COVID-19 according to World Health Organization interim guidance⁵. The demographic characteristics, clinical data, and type of antihypertensive agents used were recorded. We excluded patients under 18 years old and hypertensive patients without any medication. The ethics approval was obtained from the local ethics committee. Only cases confirmed by laboratory tests were considered positive based on a real-time reverse transcriptase-polymerase chain reaction assay of a specimen obtained from a naso- or oropharyngeal swab and were included in this study. To identify SARS-COV-2 infection, swab specimens were collected from all patients at admission and during hospitalization. The antihypertensive agents used by patients were continued during hospitalization unless contraindicated. Patients with respiratory distress (>30 breaths/min), oxygen saturation <90 at rest, under nasal oxygenation with 5-6 liters/min, arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen

(FiO₂) <300 mmHg were admitted to intensive care unit (ICU).

Statistical analysis

Descriptive analyses of the variables were expressed as mean±SD in normal distributions, and parameters with abnormal distribution were expressed as medians of the 25th-75th percentile. Categorical data were expressed as proportions. The chi-square and the Student's t-test were used for categorical and continuous variables, respectively. Fisher's exact test was applied to analyze small samples. For continuous variables, differences between the two groups were evaluated using the Student's t-test when data were normally distributed and the Mann-Whitney U test when the assumption of normality was not met. Binary logistic regression analysis was performed to determine independent factors associated with mortality. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using statistical software (SPSS 20.0, Chicago, IL, USA).

RESULTS

535 adult patients were hospitalized in the Sakarya University Education and Research Hospital with COVID-19 between March 20 and April 10, 2020. From these, we included 169 patients with a history of hypertension. The mean age of the patients was 65.8±11.7 years (range 37-96), and 90 of the patients were female (53.3%). 30 patients (17.7%) died during hospitalization and 45 (26.6%) required ICU intervention. 139 patients were discharged from hospital uneventfully. 59 of the patients (34.9%) had coexisting diabetes mellitus, 28 (16.6%) had hyperlipidemia, 25 (14.8%) had coronary artery disease, 18 (10.7%) had chronic obstructive pulmonary disease, 9 (5.3%) had cerebrovascular disease, 8 (4.7%) had chronic renal disease, 6 (3.6%) had congestive heart failure, 5 (2.9%) had malignities and 2 (1.2%) had peripheral artery disease. 142 of the patients (84%) were using ACEIs or ARBs, 91 (53.8%) were using diuretics, 69 (40.8%) were using calcium channel blockers (CCBs), 66 (39.1%) were using beta-blockers, 12 (7.1%) were using alpha-blockers and 5 (2.9%) were using mineralocorticoid receptor antagonists (MRAs) for the treatment of hypertension. The majority of the patients (131 [77.5%]) were using a combination of two or more antihypertensive agents (table 1). When we compared the type of antihypertensive agents being used between surviving

and non-surviving patients, there was no difference between the groups (Table 1). We also compared the type of antihypertensive agents between the patients with or without ICU requirement, there was no significant difference between the groups (Table 2). Binary logistic regression analysis was performed to identify independent factors associated with mortality due to COVID-19 in hypertensive patients. Age, gender, diabetes mellitus, coronary artery disease, chronic pulmonary disease, hyperlipidemia, and the type of antihypertensive agents being used were included in the equation. Age was found to be the only predictor for mortality (odds ratio=1.089, 95% confidence interval=1.038-1.142, $p<0.001$). The type of antihypertensive agent used had no effect on mortality [OR=0.527 (0.130-2.138), $p=0.370$ for ACEIs/ARBs; OR=0.731 (0.296-1.808), $p=0.498$ for CCBs; OR=0.673 (0.254-1.782), $p=0.425$ for diuretics; OR=1.846 (0.688-4.950), $p=0.223$ for beta-blockers; OR=0.389 (0.089-1.695), $p=0.208$ for alpha-blockers; and OR=1.372 (0.107-17.639), $p=0.808$ for MRAs] (Table 3).

DISCUSSION

Hypertension is one of the most frequent comorbidities among patients hospitalized for COVID-19^{6,7}. Several vascular abnormalities including widespread

microthrombotic and macrothrombotic events were frequently observed in critically ill patients with COVID-19. Potential microvascular complications caused by chronic hypertension may predispose these vascular events and worsen the prognosis and outcomes of the disease. Recent studies have claimed that hypertension is a clinically important risk factor for severe illness and mortality in COVID-19, but it is difficult to state that¹⁶. It is not clear whether the increased risk is due to hypertension itself or antihypertensive agents used. Although there are conflicting results with ACEIs and ARBs, other antihypertensive agents have not been fully evaluated for the treatment of hypertensive patients with COVID-19⁸⁻¹⁰.

The prevalence of hypertension in Turkey is approximately 27.5%¹¹. In our study, the incidence of hypertension was 29.9% in hospitalized patients due to COVID-19. Recent reports showed that hypertension is associated with poor outcomes in patients with COVID-19; however, it was also reported that hypertension was not more common in those than in the general population^{7,12}. These reports do not reveal the mechanism of this increased risk, i.e., whether it is due to hypertension itself or the antihypertensive agent used. SARS-COV-2 binds to their target cells through ACE-2, which is expressed by epithelial cells of the lung, kidney, intestine, and vessels¹³.

TABLE 1. DEMOGRAPHIC AND CLINICAL FEATURES OF HYPERTENSIVE PATIENTS WITH COVID-19.

Study population	All patients (n=169)	Non-survivors (n=30)	Survivors (n=139)	p
Age (mean±SD)	65.8±11.7	73.2±10.5	64.2±11.4	<0.001
Female gender (n, %)	90 (53.3)	15 (50)	75 (54)	0.694
Comorbidities				
Diabetes mellitus (n, %)	59 (34.9)	13 (43.3)	46 (33.1)	0.286
Hyperlipidemia (n, %)	28 (16.6)	7 (23.3)	21 (15.1)	0.272
Coronary artery disease (n, %)	25 (14.8)	8 (26.7)	17 (12.2)	0.043
Chronic pulmonary disease (n, %)	18 (10.7)	4 (13.3)	14 (10.1)	0.599
Cerebrovascular disease (n, %)	9 (5.3)	3 (10)	6 (4.3)	0.209
Chronic renal disease (n, %)	8 (4.7)	3 (10)	5 (3.6)	0.151
Congestive heart failure (n, %)	6 (3.6)	2 (6.7)	4 (2.9)	0.309
Malignities (n, %)	5 (2.9)	3 (10)	2 (1.4)	0.040
Peripheral artery disease (n, %)	2 (1.2)	2 (6.7)	0 (0)	0.031
Antihypertensive agents				
ACEIs/ARBs (n, %)	142 (84)	26 (86.7)	116 (83.5)	0.663
CCBs (n, %)	69 (40.8)	14 (46.7)	55 (39.6)	0.473
Diuretics (n, %)	91 (53.8)	19 (63.3)	72 (51.8)	0.250
Beta blockers (n, %)	66 (39.1)	9 (30)	57 (41)	0.262
Alpha blockers (n, %)	12 (7.1)	4 (13.3)	8 (5.8)	0.143
MRAs (n, %)	5 (2.9)	1 (3.3)	4 (2.9)	0.894
Combination therapy (n, %)	131 (77.5)	26 (86.7)	105 (75.5)	0.186

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCBs: calcium channel blockers, MRAs: mineralocorticoid receptor antagonists.

TABLE 2. TYPE OF ANTIHYPERTENSIVE AGENTS USED IN PATIENTS WITH OR WITHOUT INTENSIVE CARE INTERVENTION.

	With ICU intervention (n=45)	No ICU intervention (n=124)	P
ACEIs/ARBs (n,%)	38 (84.4)	104 (83.9)	0.928
CCBs (n,%)	17 (37.8)	52 (41.9)	0.627
Diuretics (n,%)	26 (57.8)	65 (52.4)	0.537
Beta blockers (n,%)	15 (33.3)	51 (41.1)	0.359
Alpha blockers (n,%)	5 (11.1)	7 (5.6)	0.221
MRAs (n,%)	1 (2.2)	4 (3.2)	0.598
Combination therapy (n,%)	34 (75.6)	97 (78.2)	0.713

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCBs: calcium channel blockers, MRAs: mineralocorticoid receptor antagonists.

The expression of ACE-2 is substantially increased in patients treated with ACEIs and ARBs. The increased expression of ACE-2 may facilitate infection by COVID-19, therefore, it is hypothesized that hypertension treatment with ACE-2-stimulating drugs increases the risk of developing severe and fatal COVID-19¹⁴. On the contrary, Zhang et al.⁴ showed that inpatient use of ACEIs or ARBs was associated with a lower risk of all-cause mortality compared with ACEI or ARBs non-users among hospitalized COVID-19 patients with hypertension. It has been hypothesized that excessive activation of RAAS might contribute to the progression of acute respiratory distress syndrome (ARDS) in patients with COVID-19 by promoting increased inflammatory response and cytokine storm¹⁵. RAAS inhibition could mitigate this effect by interfering with the negative effects of angiotensin II on ACE-2 down-regulation in infected patients. RAAS inhibitors such as ACEIs or ARBs could have a favourable impact on clinical outcomes.

Solaimanzadeh¹⁶ reported that dihydropyridine CCBs such as nifedipine and amlodipine is associated with significantly improved mortality in elderly patients hospitalized for COVID-19. They also revealed that CCBs are associated with a significantly decreased risk for intubation and mechanical ventilation¹⁶. Previous studies revealed that nifedipine and amlodipine were found to increase pulmonary vasodilation without decreasing arterial oxygenation in the treatment of pulmonary hypertension^{17,18}. Amlodipine was also found to be an effective pulmonary vasodilator agent in pulmonary hypertension secondary to chronic obstructive pulmonary disease¹⁹. Nifedipine was shown to reduce pulmonary vascular resistance and increase oxygen delivery both at rest and during exercise even in patients with normal pulmonary

TABLE 3. INDEPENDENT FACTORS ASSOCIATED WITH IN-HOSPITAL MORTALITY USING BINARY LOGISTIC REGRESSION ANALYSIS.

Variables	Exp (B) Odds ratio	95% confidence interval	P
Age, years	1.089	1.038-1.142	<0.001
Female gender	0.834	0.334-2.085	0.698
Diabetes mellitus	0.622	0.242-1.599	0.324
Coronary artery disease	0.581	0.173-1.954	0.380
Chronic pulmonary disease	1.045	0.274-3.990	0.948
Hyperlipidemia	0.525	0.154-1.785	0.302
ACEIs/ARBs	0.527	0.130-2.138	0.370
CCBs	0.731	0.296-1.808	0.498
Diuretics	0.673	0.254-1.782	0.425
Beta blockers	1.846	0.688-4.950	0.223
Alpha blockers	0.389	0.089-1.695	0.208
MRAs	1.372	0.107-17.639	0.808

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCBs: calcium channel blockers, MRAs: mineralocorticoid receptor antagonists.

artery pressures²⁰. Based on these results, they suggested that CCBs may be used as a first-line treatment in hospitalized patients with COVID-19.

Since all research on COVID-19 and antihypertensive treatment is especially focused on ACEIs and ARBs, there are not enough publications in the literature about other widely used antihypertensive agents such as beta-blockers, alpha-blockers, MRAs, and diuretics. In our study, we did not observe any effect of these antihypertensive agents on the clinical outcomes and in-hospital mortality.

Several reports revealed that ARDS in COVID-19 was associated with a strong interaction between SARS-CoV-2 and the ACE-2 receptor^{21,22}. Therefore, an increase in expression of ACE-2 receptors attached to the lung endothelium could facilitate the entrance of SARS-CoV-2 into pulmonary cells and the progression of ARDS. Although attached ACE-2 may allow SARS-CoV-2 to enter cells, its free circulating forms may inactivate SARS-CoV-2 by stopping coupling to membrane ACE-2 receptors. Spironolactone, which is the main representative of mineralocorticoid receptor antagonists, has been reported to increase ACE-2 expression in plasma²³. In contrast, it has been shown that ACEIs or ARBs have no effect on the plasma ACE-2 activity²⁴. Additionally, spironolactone does not act in pulmonary RAAS, so it could reduce ACE-2 expression on lung-cell surfaces.

In conclusion, based on the results of this current study, the type of antihypertensive agent used had no effect on the clinical course and mortality of hypertensive patients with COVID-19. The use of these agents

should be maintained for the treatment of hypertension during hospitalization. Further larger studies are needed to examine the role of these agents and their influence on the course of COVID-19.

Our study has some limitations. Firstly, this study was conducted in a single center, the study sample-size was modest and included 169 hypertensive patients. Secondly, due to the retrospective nature of this study, some parameters were not available in all patients, such as smoking habits.

RESUMO

OBJETIVO: A doença de coronavírus 2019 (COVID-19) é uma ameaça emergente à saúde causada por um novo coronavírus denominado síndrome respiratória aguda grave coronavírus 2 (Sars-COV-2). Estudos anteriores observaram que a hipertensão está associada a um aumento da mortalidade devido ao COVID-19, no entanto, não está claro se o aumento do risco pertence à própria hipertensão ou a agentes anti-hipertensivos. Nosso objetivo foi avaliar o impacto de agentes anti-hipertensivos nos resultados clínicos em pacientes hipertensos com COVID-19.

MÉTODOS: Nosso estudo incluiu 169 hipertensos consecutivos internados por COVID-19 entre 20 de março e 10 de abril de 2020. As características demográficas, dados clínicos e o tipo de anti-hipertensivos em uso foram revistos.

RESULTADOS: A idade média dos pacientes foi de 65,8±11,7 anos. Trinta pacientes (17,7%) faleceram durante a internação. Cento e quarenta e dois pacientes (84%) usavam inibidores da enzima de conversão da angiotensina (ACEIs) ou bloqueadores dos receptores da angiotensina II (ARBs), 91 (53,8%) usavam diuréticos, 69 (40,8%) usavam bloqueadores dos canais de cálcio (CCBs), 66 (39,1%) usavam betabloqueadores, 12 (7,1%) usavam bloqueadores alpha e cinco (2,9%) usavam antagonistas dos receptores de mineralocorticoides (MRAs). Não houve diferença significativa entre sobreviventes e não sobreviventes com base no tipo de agentes anti-hipertensivos em uso. A análise de regressão logística binária mostrou que o tipo de agente anti-hipertensivo utilizado não teve efeito na mortalidade (OR=0,527 (0,130-2,138), $p=0,370$ para ACEIs/ARB; OR=0,731 (0,296-1,808), $p=0,498$ para CCBs; OR=0,673 (0,254-1,782), $p=0,425$ para diuréticos; OR=1,846 (0,688-4,950), $p=0,223$ para bloqueadores beta; OR=0,389 (0,089-1,695), $p=0,208$ para bloqueadores alpha e OR=1,372 (0,107-17,639), $p=0,808$ para MRAs).

CONCLUSÃO: O tipo de agente anti-hipertensivo utilizado não teve efeito no curso clínico e na mortalidade em pacientes hipertensos com COVID-19. O uso desses agentes deve ser mantido no tratamento da hipertensão durante a hospitalização.

PALAVRAS-CHAVE: Infecções por coronavírus. Anti-hipertensivos. Hipertensão. Mortalidade hospitalar.

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