Effects of Different Anti-hypertensive Drugs on Hospitalized Patients With COVID-19 and Hypertension in China

Xia Shi
The Third People's Hospital of Shenzhen
Mengli Cao
The Third People's Hospital of Shenzhen
Shourong Liu
xixi hospital affiliated to Zhejiang Chinese Medical University
Peifen Chen
The Third People's Hospital of Shenzhen
Feng Hu
The Third People's Hospital of Shenzhen
Zhimin Su
The Third People's Hospital of Shenzhen
Siwei Jiang
The Third People's Hospital of Shenzhen
Fengxin Wang
The Third People's Hospital of Shenzhen
Yunpeng Zhang
The Third People's Hospital of Shenzhen
Hong Gao
The Third People's Hospital of Shenzhen
Yingxia Liu (yingxialiu@hotmail.com)
Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen, Guangdong, China https://orcid.org/0000-0001-6335-3346

Research

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Abstract

Background and aims: Calcium channel blockers (CCBs) and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are commonly used in the treatment of hypertension. However, it is still not clear whether there are differences among different anti-hypertensive drugs in the treatment of patients with coronavirus disease 2019 (COVID-19) and hypertension. Herein, we aimed to assess the relation between different anti-hypertensive medications and COVID-19 outcomes.

Materials and methods: We conducted a retrospective analysis of 58 hypertensive patients with COVID-19 who were treated with different anti-hypertensive drugs and reviewed the clinical data obtained from electronic medical records, including epidemiological, clinical, laboratory, and the treatment and progression of the disease.

Results: There was no obvious difference in clinical prognosis after using any anti-hypertensive drugs in patients with COVID-19 and hypertension, but the different anti-hypertensive drugs were associated with the use of non-invasive ventilator treatment at admission comparing two groups between ACEIs/ARBs and CCBs+ACEIs/ARBs.

Conclusion: there is no evidence showing that the different use of anti-hypertensive drugs is related to outcomes of patients with COVID-19 and hypertension, even between single drug regimen and combined therapy (with at least two anti-hypertensive drugs as combined therapy).

Introduction

On 30 January 2020, the World Health Organization (WHO) announced the novel coronavirus epidemic, which is now named coronavirus disease 2019 (COVID-19), a public health emergency of international concern. By 29 Sep 2020, there have been more than 33 million people that are diagnosed with lab-confirmed COVID-19 and 998696 deaths accumulated globally[1].

A large number of studies have demonstrated the important roles of the renin-angiotensin system (RAS) in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which exploited the angiotensin-converting enzyme 2 (ACE2) receptor for entry into target cells and cause vasoconstrictive, pro-inflammatory, and pro-oxidative effects[2]. According to the latest reports, hypertension has been widely associated with increasing disease severity[1, 3–5]. In view of the above reasons, the relation between anti-hypertensive medications and COVID-19 outcomes is very important to public health.

The hypertension patients are basically treated with anti-hypertensive drugs, mainly including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs) and so on. As early as February this year, our team proposed that a number of potential diagnosis biomarkers and angiotensin receptor blocker (ARB) drugs for potential repurposing treatment of COVID-19 infection, and therapy with ARB might substantially reduce the risk of COVID-19 severe disease[6–7]. In addition, previous studies have also shown that CCBs not only regularly used to treat hypertension, but also used as medications to treat various pulmonary disorders with vasoconstriction, such as pulmonary hypertension and so on[8–9].

However, it remains unclear that which regimen composites of different anti-hypertensive drugs are highly relevant to clinical prognosis. What should be done in regard to the different anti-hypertensive treatment of patients with COVID-19 complicated by hypertension? In the present study, we investigated the clinical and laboratory characteristic of the hospitalized COVID-19 patients with hypertension, and compared the prognosis discrepancy in different anti-hypertensive drug groups. This study will provide clinical insights into the impact of different anti-hypertensive drugs on the clinical course of COVID-19 infection.

Methods

Data collection

In the current study, data from all consecutively hospitalized patients from 11 January 2020 to 17 April 2020 at the Third People's Hospital of Shenzhen and Xixi Hospital of Hangzhou in China were collected. The Third People's Hospital of Shenzhen is the only one designated hospital authorized by the government in Shenzhen City to take care of COVID-19 patients, while Hangzhou Xixi

Hospital is also the first designated hospital for diagnosis and treatment of COVID-19 in Hangzhou. This study was approved by the Shenzhen Third People's Hospital Ethics Committee. Verbal informed consents were obtained from all patients or patients' family members. The information on patients(age > = 50 years old)with hypertension was studied separately among all enrolled COVID-19 patients. We reviewed the clinical data obtained from electronic medical records, including epidemiological, clinical, laboratory, and the treatment and progression of the disease. All patients with COVID-19 were validated by the key laboratory of the Shenzhen or Hangzhou Center for Disease Control and Prevention, and their data were collected by nurses, physicians or other health-care staff at the hospital.

The primary endpoint was mortality caused by all reasons during hospitalization. Other endpoints include the time interval between symptoms onset and discharge, the frequency of invasive mechanical ventilation use, and the severity of COVID-19 disease. The severity of COVID-19 was categorized as mild, severe, or critical. Mild included non-pneumonia and mild pneumonia cases. Severe was characterized by dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO2/FiO2 ratio ≤ 300, and/or lung infiltrates > 50% within 24–48 h. Critical cases were defined as respiratory failure requiring mechanic ventilation, septic shock, and/or multiple organ dysfunction/failure[10].Patients with hypertension were classified based upon clearly documented medical history with systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg[11].

Statistical analyses

The SPSS 18.0 software package was used for statistical analysis. Continuous data accorded with normal distribution were expressed as mean ± SD and compared by independent samples t-test. Count data are expressed as percentages, and the difference between groups was tested by the Chi-square test. $P < 0.05$ was considered statistically significant.

Results

A total of 73 patients with COVID-19 and hypertension were identified. Of these, 7 patients were excluded since they have not been treated with either CCBs or ACEIs/ARBs, another 8 patients were excluded since their age was under 50. The enrolled patients, including 32 males (55%) and 26 females (45%), were treated with one or multiple anti-hypertensive drugs, including ACEIs/ARBs, CCBs and so on. Then, they were divided into 3 subgroups based on anti-hypertensive drug treatments. The CCBs group is comprised of patients treated with sole CCBs; while the ACEIs/ARBs group consists of patients treated with ACEIs or ARBs, but not CCBs; the CCBs+ ACEIs/ARBs group harbors patients treated with two anti-hypertensive drugs, one is CCBs, another is ACEIs or ARBs.

Demographic data, comorbidities and Severity of illness in different groups

The results of demographic data, comorbidities and severity of illness in these groups were analyzed. In spite of difference in the age of patients treated with CCBs or CCBs+ACEIs/ARBs, there is no significant difference in the clinical severity comparing with different groups. The specific information are shown in the table 1 below.

Patients using ventilator in different groups

We then investigated the ventilator usage in different groups. The result showed that no patients received any ventilator treatment in the CCBs+ACEIs/ARBs group, indicating significantly better pulmonary function compared to other groups ($P<0.05$). The specific information of the patients comparing in different groups are shown in the table 2 below.

Supplementary measures in different groups

Since some other factors may affect the final result, multiple supplementary treatment have been recorded, such as broad-spectrum antibiotics, Extra-corporeal Membrane Oxygenation (ECMO) and Continuous Renal Replacement Therapy (CRRT), which are usually used for the treatment of severe or critical COVID-19 cases with bacterial infections, cardiopulmonary failure or renal failure. The number of patients receiving these additional treatment was indicated, and all the data signed no difference among groups, suggesting that different anti-hypertension drug usage strategies do not correlate with other supplementary treatment (Table 3).

Clinical Data in different groups at initial presentation to hospital

Finally, other clinical features, including vital signs and laboratory findings, were compared among these three groups. The indexes showed that there was no overt difference except the systolic blood pressure between the CCBs and ACE Is/ARBs at admission (Table 4).

Discussion

Currently, the novel coronavirus (COVID-19) has spread to many countries around the world. It has been demonstrated that hypertension, the most common comorbidity in COVID-19 patients, is predisposed to develop severe cases, especially in the older individuals[12].By above reasons, we enrolled 58 patients over 50 years old in the population. Besides, hypertension may be involved in the pathogenesis of COVID -19 either by playing a direct role as a pre-existing clinical predictor of disease severity or by contributing to deterioration in the later course of the disease characterized by acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and / or multiple organ failure (MOF) [12].

anti-hypertensive drugs are ones of the most widely used pharmacologic agents in the world and is they are predominantly used in the elderly subjects. The essential hypertension patients are basically treated with blood pressure lowering drugs including RAS blockers (ACEIs/ARBs), CCBs and so on.

In fact, our team firstly demonstrated that the plasma AngII concentration was significantly elevated after severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection. Lei Fang and his colleagues also showed that coronavirus would probably use angiotensin converting enzyme 2 (ACE2) to target cells on the epithelium of the lungs, intestine, kidneys, and blood vessels[12].Moreover, circulating amounts of ACE2 increased in patients with hypertension or diabetes, and levels are further increased by different drugs, including ACEIs and ARBs[13–14].It should also be emphasized that specific alleles control ACE2 expression, activity, and response to ACEIs[13].In addition to animal models, humans given ACEIs, ARBs, or both, had increased ACE2 levels on intestine luminal cells[15].Nevertheless, it is still controversial about the ACEIs/ARBs as treatment of COVID-19. Besides, whether ACE2 expression is upregulated by either of these drugs in the primary target cells of SARS-CoV-2 in human lungs is not yet known. A number of scientists have showed that ACEI and ARB pharmacotherapy may aggravate SARS-CoV-2-induced lung disease by increasing ACE2 surface expression on airway epithelial cells[12, 16], while it also has been reported that ACEI/ARB exposure was not associated with a higher risk of COVID-19 infection[16–17],or even had the benefit for prognosis[18].On the other hand, some researchers have recommended CCBs as a suitable alternative treatment to renin-angiotensin-aldosterone system inhibitors, because the CCBs have not been reported to increase the expression of ACE2, Thus, the CCBs are not only used in the clinical management of hypertension, but also utilized in the treatment of various pulmonary disorders with vasoconstriction. The utilization of CCBs rather than RAS blockers is particularly recommended for elderly Chinese hypertensive population to reduce the risk of stroke, which is the major cardiovascular risk threatening the Chinese hypertensive population[19–20].It has also been confirmed that nifedipine and amlodipine were found to be associated with significantly improved mortality and a decreased risk for intubation and mechanical ventilation in elderly patients with COVID-19[21].

In recent a few months, we have collected the data of patients with COVID-19 and hypertension, and then analyzed clinical characteristics of 58 enrolled patients, we observed that there was no obvious difference in clinical course in ACEIs/ARBs medication, CCBs medication and the drug-usage-combined group (CCBs and ACEI/ARB_S) It may be attributed to several factors: First, several works have already stressed the fact that blood pressure control has no effect on susceptibility to the SARS-CoV-2 viral infection[22].The higher prevalence of hypertension in patients with COVID-19 is more likely due to the fact that the severe patients were significantly older. Besides, the major complications of hypertension such as chronic heart failure, cerebral infarction and chronic renal failure made the patient much more vulnerable to progression to severe infection or death. Second, combined with previous autopsies, it was confirmed that the lungs were the main target organs invaded by novel coronavirus while the structure of cardiomyocytes was often intact. There was only a small amount of monocyte inflammatory infiltration in the interstitium[23–24], indicating that the lung may be the main infection site of COVID-19. Therefore,the outcomes of patients with COVID-19 and hypertension mostly were determined by the functional recovery of the primary underlying disease, especially the pulmonary function. Our preliminary work supported this point[25].Third, reviewing retrospective research data about the

reports associating hypertension with COVID-infection, it has been recognized that the prevalence of hypertension in adults was around that same percentage of the COVID-19 patients[3].

In addition, there was also significantly difference in the use of non-invasive ventilator treatment at admission with different groups (ACEIs/ARBs group and CCBs + ACEIs/ARBs group). Reviewing retrospective research data, CCBs have been utilized in the treatment of various pulmonary disorders with vasoconstriction as well, while dysregulation or loss of hypoxic pulmonary vasoconstriction is suspected in patients with COVID-19. This could potentially explain the significant difference of clinical data at the use of non-invasive ventilator treatment. But this remains to be validated by more rigorous studies due to the relatively small sample size. Meanwhile, we found that of the usage of non-invasive ventilator treatment was not associated with the final clinical ending of patients. The mortality rate of novel coronavirus in China was much lower than that of other countries[4, 26], so we speculated that it was likely due to the early detection, early treatment, and the use of various adjuvant treatments.

In conclusion, the different use of anti-hypertensive drugs does not affect outcomes of patients with COVID-19 and hypertension, even between single drug regimen and combined therapy (with at least two anti-hypertensive drugs as combined therapy).The use or temporary adjustment of antihypertension drugs during infectious disease could be individualized according to volume status, hemodynamic stability, comorbid cardiovascular disease profiles, and anti-hypertensive drug class. More researches are needed for the use of anti-hypertensive drugs before and during severe infection or epidemics.

Conclusions

Based on our research, there is no evidence showing that the different use of anti-hypertensive drugs is related to outcomes of patients with COVID-19 and hypertension, even between single drug regimen and combined therapy (with at least two anti-hypertensive drugs as combined therapy).Therefore, We suggest that it may be better for patients with COVID-19 and hypertension to continue to use the original antihypertensive regimen routinely.

Abbreviations

COVID-19
coronavirus disease 2019
CCBs
Calcium channel blockers
ACEIs
angiotensin-converting enzyme inhibitors
ARBs
angiotensin receptor blockers
ACE2
angiotensin converting enzyme 2

Declarations

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Not applicable.

Competing interests

Not applicable.

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Authors' contributions

YL, HG and XS conceived the study and guided the project.MC, PC, FH, YP, FW and ZS collected clinical data from medical records of 2019-nCoV infected patients admitted in Shenzhen Third People's Hospital; SL collected clinical data from medical records of 2019-nCoV infected patients admitted in Xixi Hospital Affiliated to Zhejiang Chinese Medical University.SJ and YZ led clinical data statistical analysis and meta-analysis.YL, XS wrote the manuscript. The final version of manuscript was approved by all the authors.

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Authors' information

[1] Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen, Guangdong, China

[2] Xixi Hospital Affiliated to Zhejiang Chinese Medical University Hangzhou, Zhejiang, China;

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Tables

Table 1. Demographic data, comorbidities and Severity of illness in different groups

	CCBs(n=34)	ACE Is/ARBs(n=14)	CCBs+ACEs I/ARBs(n=10)	*P*-value(CCBs vs ACE Is/ARBs)	*P*-value(CCBs vs CCBs+ACE Is/ARBs)	*P*-value(ACE Is/ARB svs CCBs+ACE Is/ARBs)
age years	64.12±6.83	65.36±5.50	60.20±8.68	NS	0.01	NS
sex						
female	13	9	4	NS	NS	NS
male	21	5	6	NS	NS	NS
other comorbidities						
Arrhythmia	0	1	0	NS	NS	NS
diabetes	5	3	1	NS	NS	NS
Bronchial Asthma or Chronic Obstructive Pulmonary Disease	3	1	0	NS	NS	NS
Cerebrovascular disease (stroke or TIA)	0	0	0	NS	NS	NS
hyperlipidemia	1	0	0	NS	NS	NS
Hyperuricemia	1	1	0	NS	NS	NS
heart failure	1	0	0	NS	NS	NS
coronary artery disease	4	0	1	NS	NS	NS
history of coronary artery bypass graft	1	1	1	NS	NS	NS
Peripheral atherosclerosis	2	0	0	NS	NS	NS
Valvular heart disease	0	2	0	NS	NS	NS
history of cancer	1	0	1	NS	NS	NS
Thyroid dysfunction	1	0	0	NS	NS	NS
Abnormal autoimmune function.	0	0	1	NS	NS	NS
Hepatitis B or fatty liver	0	2	1	NS	NS	NS
Clinical severity						
Mild	20	7	7	NS	NS	NS
Severe	11	6	3	NS	NS	NS
Critical	3	1	0	NS	NS	NS
deaths	1	0	0	NS	NS	NS

Abbreviations: NS= not significant

Table 2 Patients using ventilator in different groups

	CCBs(n=34)	ACE Is/ARBs(n=14)	CCBs+ACEIs/ARBs(n=10)	*P*-value(CCBs vs ACE Is/ARBs)	*P*-value(CCBs vs CCBs+ACE Is/ARBs)	*P*-value(ACE Is/ARBs vs CCBs+ACE Is/ARBs)
Number of Patients Intubated and Mechanically Ventilated	3	1	0	NS	NS	NS
Number of patients using non-invasive ventilator	8	5	0	NS	NS	0.03*

Abbreviations: NS= not significant

* indicates significance at $p<0.05$.

Table 3 Supplementary measures in different groups

	CCBs(n=34)	ACE Is/ARBs(n=14)	CCB+ACEIs/ARBs(n=10)	*P*-value(CCBs vs ACE Is/ARBs)	*P*-value(CCBs vs CCBs+ACE Is/ARBs)	*P*-value(ACE Is/ARBs vs CCBs+ACE Is/ARBs)
Broad-Spectrum Antibiotics	11	7	2	NS	NS	NS
ECMO	1	1	0	NS	NS	NS
CRRT	2	1	0	NS	NS	NS
Methylprednisolone	2	4	0	NS	NS	NS
Vasoactive drugs	1	1	0	NS	NS	NS

Abbreviations: NS= not significant

Table 4 Clinical Data in different groups at initial presentation to hospital

	CCBs(n=34)	ACE Is/ARBs(n=14)	CCBs+ACE Is/ARBs(n=10)	*P*-value(CCBs vs ACE Is/ARBs)	*P*-value(CCBs vs CCBs+ACE Is/ARBs)	*P*-value(ACE Is/ARBs vs CCBs+ACE Is/ARBs)
Temperature	37.12±0.72	37.18±0.82	36.69±0.24	NS	NS	NS
respiratory rate	20.07±1.21	20.78±1.20	20.89±1.96	NS	NS	NS
Heart rate	87.36±13.03	83.11±10.82	81.00±17.59	NS	NS	NS
Systolic Blood Pressure	146.18±16.38	133.36±19.54	141.60±18.71	0.02*	NS	NS
Diastolic Blood Pressure	86.5±14.00	83.86±7.10	84.00±13.02	NS	NS	NS
PaO2/FiO2	400.75±119.89	364.07±82.85	352.50±143.38	NS	NS	NS
PCT	0.083±0.08	0.05±0.03	0.05±0.01	NS	NS	NS
WBC($\times 10^9$ L^{-1})	6.7±2.53	8.09±3.92	6.51±2.57	NS	NS	NS
LYM($\times 10^9$ L^{-1})	1.40±0.62	1.59±1.01	1.35±0.36	NS	NS	NS
AST(U L^{-1})	47.25±122.70	31.39±12.07	22.78±7.99	NS	NS	NS
ALT(U L^{-1})	47.63±91.11	34.94±20.43	29.24±12.08	NS	NS	NS
MYO (ng mL^{-1})	68.08±95.73	45.29±15.46	44.96±33.38	NS	NS	NS
CK (ng mL^{-1})	68.13±49.93	85.30±59.06	76.49±103.80	NS	NS	NS
D-Dimer (ng mL^{-1})	1.20±2.65	2.32±5.33	0.61±0.37	NS	NS	NS

Abbreviations: NS= not significant

* indicates significance at $p<0.05$.