Received: 21 October 2020 | Accepted: 26 February 2021

DOI: 10.1111/ijcp.14124

ORIGINAL PAPER

INFECTIOUS DISEASES

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hypertension: A randomised clinical trial

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Funding information
Tabriz University of Medical Sciences, Grant/Award Number: 65204

Abstract

Background: Controversy exists regarding the drug selection in hypertension (HTN) management in patients with COVID-19. This study aimed to compare the effects of losartan and amlodipine in patients with primary HTN and COVID-19.

Methods: In this randomised clinical trial, hospitalised patients with COVID-19 and primary HTN were enrolled in the study. One arm received losartan, 25 mg, twice a day and the other arm received amlodipine, 5 mg per day for 2 weeks. The main outcomes were compare 30-day mortality rate and length of hospital stay.

Results: The mean age of patients treated with losartan (N = 41) and amlodipine (N = 39) was 67.3 ± 14.8 and 60.1 ± 17.3 years, respectively (*P* value = .068). The length of hospital stay in losartan and amlodipine groups was 4.57 ± 2.59 and 7.30 ± 8.70 days, respectively (*P* value = .085). Also, the length of ICU admission in losartan and amlodipine group was 7.13 ± 5.99 and 7.15 ± 9.95 days, respectively (*P* value = .994). The 30-day mortality was two and five patients in losartan and amlodipine groups, respectively (*P* value = .241).

Conclusions: There was no priority in losartan or amlodipine administration in COVID-19 patients with primary HTN in decreasing mortality rate, hospital and ICU length stay. Further studies need to clarify the first-line anti-HTN medications in COVID-19.

What's known

- Hypertension is a major disease that increases the risk of acute respiratory failure, hospital admission and mortality rate among patients with COVID-19.
- Controversy exists regarding the drug selection in hypertension management in patients with COVID-19.

What's new

- There was no priority in losartan or amlodipine administration in COVID-19 patients with primary HTN in decreasing mortality rate.
- There was no priority in losartan or amlodipine administration in COVID-19 patients with primary HTN in decreasing hospital length stay.
- There was no priority in losartan or amlodipine administration in COVID-19 patients with primary HTN in decreasing ICU length stay.

1 | INTRODUCTION

Several underlying medical conditions are associated with increasing the risk of COVID-19 severity and are associated with a higher mortality rate.[1-3] Hypertension (HTN) is a major disease that increases the risk of acute respiratory failure, hospital admission and mortality rate among patients with COVID-19.[4,5] It is a main co-morbidity among patients with COVID-19 and management of HTN in COVID-19 is an essential for reduction of mortality and morbidity. In contrary, a recent hypothesis highlights no association between HTN treatment with RAAS inhibitors and unfavourable outcomes in COVID-19.[6]

The primary therapeutic strategy for the management and monitoring of HTN are some of renin-angiotensin-aldosterone system (RAAS) inhibiting molecules such as angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs).[7-9] The expression of angiotensin-converting enzyme (ACE) II has been proposed to be increased by the activation of ACE inhibitors (ACEIs) and ARBs. Therefore, over the COVID-19 pandemic, susceptibility to severe infection can be reduced.[10,11] Although it has been suggested the ACEIs counter the anti-inflammatory effects of ACE2, direct inhibitory efficacy of ACE against the ACE2 has not been proved in experimental surveys.[12,13] Accordingly, there is a controversy in the successive use of ACEI/ARB in the patients with COVID-19, which emphasises that ACEIs and ARBs may promote the ACE2 receptor expression in the animal trials and some others suggest these drug classes as an additional therapy for COVID-19 treatment.[14,15] Therefore, it seems that the ARBs and ACEIs are two-edged swards in COVID-19 management and some studies were recommended CCBs as an alternative treatment in patients with HTN and COVID-19.[10]

An antagonist of angiotensin I type 1 receptor called losartan is considered as an effectively strong drug for the treatment of such cases.[16,17] Novel investigations suggest the maturation of dendritic cells, impairment of T-helper 1 immune response can be impeded by losartan which eventually reduces the inflammatory procedures induced by angiotensin II.[18,19] Nevertheless, the losartan defensive mechanisms in acute lung injury have not yet been fully understood.

Beneficial or harmful effects of anti-hypertension medications in patients with COVID-19 and primary HTN are still unclear. On the contrary, there are controversy in best-choice medication in patients with primary HTN and COVID-19. Therefore, this study aimed to compare the effects of losartan and amlodipine in patients with COVID-19 and primary HTN.

2 | METHODS

2.1 | Study design

The current study was a prospective randomised clinical trial in order to compare the effects of losartan and amlodipine in primary HTN management of patients with COVID-19. The study was approved by the Medical Ethical Committee of Tabriz University of Medical Sciences and was registered at Iranian Registry for Clinical Trials (IRCT ID: IRCT20180802040678N4) on 1 April 2020. Informed consent was obtained from patients before enrolment.

2.2 | Study participants

Patients with COVID-19 and primary HTN were recruited to the study in Imam Reza Hospital of Tabriz University of Medical Sciences in Tabriz, Iran, from 2 April 2020 to 30 June 2020.

Based on the COVID-19 pneumonia prevention and control program (5th edition) publishing by the national health commission of world health organization (WHO) guidance, COVID-19 was detected through the reverse transcription-polymerase chain reaction (RT-PCR)[20] (ICD code: U07.1).

Inclusion criteria were the following: age 18 years and older, patients with primary HTN with systolic blood pressure (SBP) level of 130-140 mmHg and diastolic blood pressure (DBP) of 85-90 mmHg who were managed by non-pharmacological strategies or were newly diagnosed.

Exclusion criteria were pregnant and lactating patients, severe hepatic and renal failure, bilateral renal artery stenosis and patients with the history of uncontrolled HTN, and also patients showing losartan side effects such as cough exacerbation, increased potassium levels in blood and baseline, new anaemia, shock or reduction of blood pressure 90/60 mmHg or less, all had been excluded.

2.3 | Randomisation

The patients were randomised (randomly assigned 1:1) according to inclusion and exclusion criteria and via block randomisation in both groups. Randomisation was done by a computer-generated

random number for the assignment of participants to the losartan or amlodipine arm. A researcher who was not involved in our survey conducted the allocation in order to maintain blinding. Till the achievement and assessment of all data, submitted cases who received drug administration and analysing the results remained blind via randomised and allocated processes.

2.4 | Drug treatment

Besides standard treatment, supportive and symptomatic therapy in both groups, in losartan group patients was received 25 mg losartan (Actoverco, Karaj, Iran) tablets twice per day (before breakfast and after dinner) and in amlodipine group patients was received amlodipine besilate 5 mg (Actoverco, Karaj, Iran) per day at least for 14 days. In intubated patients, the drugs were continued using nasogastric tube. The study design is shown in Figure 1.

2.5 | Data collection

In the primary examination by a pulmonologist, demographic data including age and sex, and also medical history or co-morbidities were extracted. Furthermore, clinical characteristics were also obtained.

In all cases, chest computed tomography (CT) scan was done, and before commencing the interview, all laboratory information were collected.

2.6 | Primary and secondary outcomes

In this study, the primary outcomes were comparison of 30-days mortality and length of hospital stay between groups. The secondary outcomes were disease severity assessment, needs to intubation, laboratory and clinical parameters change. Disease severity was assessed by sequential organ failure assessment

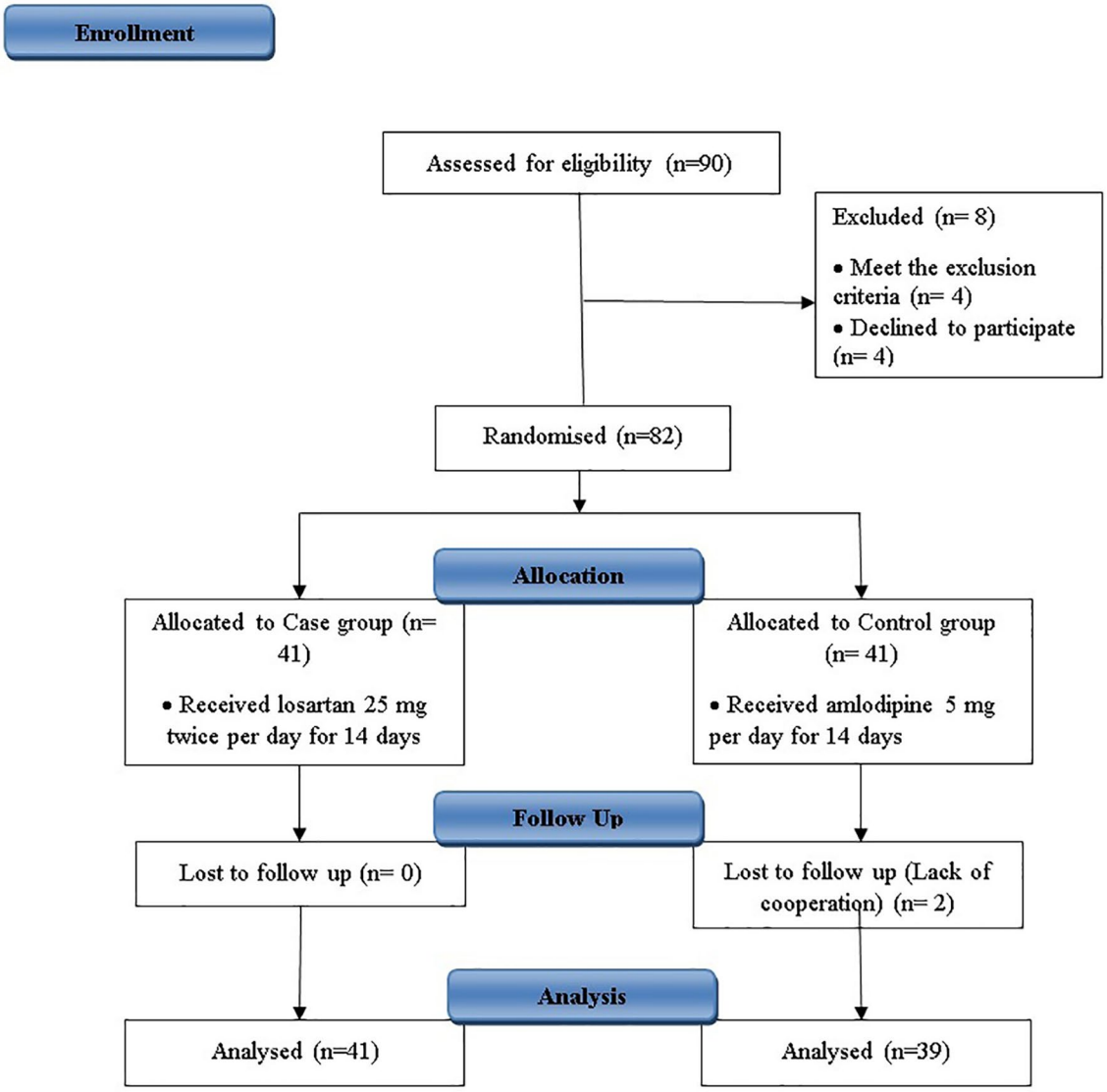

FIGURE 1 Study flow diagram

(SOFA) respiratory score. The SOFA assessment is used to assess of critical patients to determine the extent of organ function or rate of failure. Total score is calculated by a SOFA calculator. Total scores range are from 0 to 24, with higher scores indicating greater chance of mortality.[21]

2.7 | Statistical analysis

The normal distribution of variables was evaluated using the Kolmogorov-Smirnov test. Qualitative and normally distributed quantitative variables were displayed as numbers (percentages) and mean ± standard deviation, respectively. Paired *t* test was utilised to compare the differences between variables before and after the drug consumption. Chi-squared or independent sample t-test was also used for differences between groups. *P* value < .05 was considered statistically significant. Data were analysed using SPSS, 24.0 (SPSS Inc, Chicago, IL).

3 | RESULTS

3.1 | Characteristics of participants

A total of 82 patients with COVID-19 and primary HTN were included in the study. Finally, 41 (mean age 67.3 ± 14.8, 53.7% men) were in the losartan group and 39 (mean age 60.1 ± 17.3, 53.8% men) in the amlodipine group were analysed. There was no significant age (*P* value = .068) and sex (*P* value = .232) difference between the two groups. Baseline characteristics of patients are summarised in the Table 1. The blood pressure, pulse rate, respiratory rate, body temperature and O_2 saturation of patients are shown in the Table 1.

TABLE 1 Baseline characteristics of patients

Variable	Losartan	Amlodipine
Age (y)	67.3 ± 14.8	60.1 ± 17.3
Gender (n)		
Male	22 (53.7%)	19 (46.3%)
Female	21 (53.8%)	18 (46.2%)
Smoking (n)	5 (12.2%)	6 (15.4%)
Medical history (n)		
Diabetes mellitus	11	8
Cardiovascular diseases	8	7
COPD/Asthma	5	7
Hyperlipidaemia	4	3
Imaging findings (n)		
Ground-glass opacity	27 (65.9%)	31 (79.5%)
Consolidation	7 (17.1%)	5 (12.8%)
Mix pattern	7 (17.1%)	3 (7.7%)

3.2 | Primary outcomes

Of the patients in the losartan group, 39 (95.1%) were survived and 2 (4.9%) were died. In addition, eight patients (19.5%) were intubated in this group. In the amlodipine group, 34 patients (87.18%) were discharged and 5 patients (12.82%) were died. Also, nine patients (23.08%) were intubated in this group. Morewise, the mean duration of hospitalisation in losartan group was 4.57 ± 2.59 while the mean duration of hospitalisation in amlodipine group was 7.30 ± 8.70 days, that shows more days hospitalisation in controls (*P* value = .085). Also the length of ICU admission in losartan group was 7.13 ± 5.99 days, while it was 7.15 ± 9.95 days in the amlodipine group that shows more length of ICU admission in amlodipine group (*P* value > .05). Comparison of outcomes is shown in Table 2.

3.3 | Secondary outcomes

Characteristics of patients before and after intervention in both groups including cell blood counts, electrolyte profiles, liver and kidney function tests, inflammatory parameters and blood gas analysis are shown in Table 3.

In the losartan group, the mean admission- and discharge-time SOFA score were 3.08 ± 1.35 and 2.42 ± 1.17, respectively (*P* value = .002). In the amlodipine group, the mean admission- and discharge-time SOFA score was 3.74 ± 2.21 and 4.26 ± 3.71, respectively (*P* value = .326). The comparison of these groups highlighted no significant difference in disease severity between groups at discharge time (*P* value = .084).

TABLE 2 Disease severity, length of admission and mortality in two groups

Variables	Group	Mean ± SD	*P* value
SOFA score, d	Baseline		
	Losartan	3.08 ± 1.35	.954
	Amlodipine	3.74 ± 2.21	
	At Discharge		
	Losartan	2.42 ± 1.17	.084
	Amlodipine	4.26 ± 3.71	
Length of admission, d	Losartan	4.57 ± 2.59	.085
	Amlodipine	7.30 ± 8.69	
Length of ICU admission, d	Losartan	7.13 ± 5.99	.994
	Amlodipine	7.15 ± 9.95	
30-d mortality	Losartan (n)		
	Cure	39	.241
	Death	2	
	Amlodipine (n)		
	Cure	34	
	Death	5	

TABLE 3 Clinical and laboratory findings before and after the intervention

Variables	Losartan group (n = 41)	Amlodipine group (n = 39)	P^b
Systolic blood pressure (mmHg)			
Baseline	132.24 ± 4.22 (130-141)	133.41 ± 3.81 (130-139)	.287
At discharge	114.16 ± 10.19 (101-139)	109.62 ± 9.74 (99-130)	.103
P^a	<.001	<.001	—
Diastolic blood pressure (median of day), (mmHg)			
Baseline	86.55 ± 2.81 (85-100)	86.86 ± 2.64 (85-97)	.642
In discharge	72.28 ± 7.59 (63-90)	72.14 ± 7.51 (62-94)	.925
P^a	<.001	.077	—
Pulse rate (n)			
Baseline	93.8 ± 15.791 (62-130)	87.79 ± 14.944 (58-120)	.113
In discharge	87.86 ± 10.497 (60-105)	84.38 ± 9.584 (64-105)	.218
P^a	.020	.658	—
Respiratory rate (n)			
Baseline	22.12 ± 7.295 (10-55)	22.46 ± 5.281 (16-38)	.832
In discharge	15.31 ± 4.516 (8-26)	17.29 ± 1.961 (14-20)	.032
P^a	.001	.002	—
Body temperature (°C)			
Baseline	36.741 ± 1.7671 (26.5-39)	37.024 ± 0.4771 (36-38.2)	.405
In discharge	36.511 ± 0.6098 (34.3-39)	36.571 ± 0.1678 (36.5-37.2)	.660
P^a	.820	<.001	—
O_2 saturation (%)			
Baseline	86.49 ± 8.62 (60-96)	87.52 ± 11.089 (40-96)	.664
In discharge	91.65 ± 5.453 (72-96)	94.11 ± 2.158 (90-99)	.020
P^a	.010	.019	—
White blood cell count (n)/μL			
Baseline	8807.32 ± 4675.435 (3300-22300)	8186.21 ± 3567.184 (2700-15400)	.602
In discharge	23 269.57 ± 67 747.78 (1100-333000)	12 936.84 ± 18 713.49 (5100-89000)	.524
P^a	.331	.238	—
Neutrophil (%)			
Baseline	77.5 ± 12.4308 (55-100)	76.79 ± 9.2999 (57.3-93)	.787
In discharge	82.687 ± 8.7714 (63.7-96.8)	77.372 ± 15.5331 (41.6-96)	.206
P^a	.171	.934	—
Lymphocyte (%)			
Baseline	17.32 ± 11.1105 (4.5-40.1)	17.703 ± 8.4144 (2-35.2)	.876
In discharge	11.813 ± 8.2195 (0.7-33.4)	15.422 ± 12.768 (2.1-51.3)	.279
P^a	.018	.415	—
Platelet (n)/μL			
Baseline	208 012 ± 77 957 (94000-474000)	217 276 ± 83 963 (84000-437000)	.637
In discharge	216 166 ± 83 766 (95000-400000)	234 052 ± 94 862 (87000-424000)	.516
P^a	.865	.243	—
Haemoglobin (g/dL)			
Baseline	12.676 ± 2.1436 (8.8-18.1)	12.862 ± 2.0491 (7.5-15.9)	.716
In discharge	11.761 ± 2.2259 (8-15.7)	12.032 ± 2.5151 (8.3-15.8)	.714
P^a	.219	.029	—
MPV			
Baseline	10.131 ± 1.2455 (7.9-14.2)	13.116 ± 16.6717 (8.4-930	.381

(Continues)

TABLE 3 (Continued)

Variables	Losartan group (n = 41)	Amlodipine group (n = 39)	P^b
In discharge	10.659 ± 1.482 (8.6-14.5)	15.213 ± 22.6369 (8.5-97)	.450
P^a	.152	.905	—
RDW			
Baseline	14.237 ± 2.3369 (10-20.4)	14.208 ± 2.2692 (11.2-21.80)	.933
In discharge	14.682 ± 2.4521 (11.5-19.9)	14.362 ± 1.6661 (11.9-16.5)	.689
P^a	.726	.622	—
Creatinine (mg/dL)			
Baseline	2.9637 ± 7.90698 (0.6-47)	2.8993 ± 8.3426 (0.55-46)	.974
In discharge	2.7632 ± 7.37937 (0.69-38)	3.9 ± 10.73347 (0.6-48)	.679
P^a	.993	.474	—
Urea (mg/dL)			
Baseline	38.691 ± 17.9744 (1.1-86)	44.272 ± 46.2101 (0.9-199)	.541
In discharge	45.241 ± 24.947 (1.3-93)	55.272 ± 48.8724 (1.2-206)	.403
P^a	.263	.588	—
Sodium (mEq/L)			
Baseline	138.43 ± 3.071 (133-148)	136.86 ± 3.193 (128-142)	.069
In discharge	139.9 ± 3.145 (136 −146)	138.26 ± 3.619 (129-143)	.133
P^a	.807	.314	—
Potassium (mEq/L)			
Baseline	4.187 ± 0.4328 (3.2-4.9)	4.269 ± 0.4878 (3.4-5.2)	.467
In discharge	4.129 ± 0.4014 (3.2-4.6)	4.184 ± 0.7198 (2.5-5.5)	.761
P^a	.056	.705	—
Calcium (mg/dL)			
Baseline	7.4514 ± 2.86195 (1.05-10.1)	8.0415 ± 2.14416 (0.89-9.8)	.371
In discharge	7.4017 ± 2.90453 (1.03-9.4)	8.7375 ± 0.51624 (7.6-9.5)	.071
P^a	.856	.224	—
Magnesium (mg/dL)			
Baseline	2.145 ± 0.531 (1.3-4.1)	1.985 ± 0.4213 (1.2-2.7)	.182
In discharge	2.505 ± 0.7153 (1.6-4.2)	2.119 ± 0.2257 (1.8-2.5)	.036
P^a	.040	.333	—
Phosphate (mg/dL)			
Baseline	2.611 ± 0.7328 (1.4-4.4)	2.733 ± 0.8195 (1.3-4.4)	.536
In discharge	2.689 ± 0.5005 (1.9-3.5)	2.5 ± 0.6047 (0.9-3.4)	.343
P^a	.772	.685	—
Aspartate aminotransferase (U/L)			
Baseline	39.51 ± 35.08 (9-168)	31.07 ± 14.684 (11-58)	.237
In discharge	40.21 ± 28.913 (10-110)	31.67 ± 17.975 (13-75)	.325
P^a	.184	.592	—
Alanine aminotransferase (U/L)			
Baseline	27.73 ± 14.689 (11-67)	24.64 ± 15.863 (9-87)	.421
In discharge	30.68 ± 12.641 (10-51)	22.93 ± 12.792 (11-60)	.087
P^a	.796	.783	—
Alkaline phosphatase (U/L)			
Baseline	205.62 ± 124.161 (32-729)	326.14 ± 524.88 (69-2610)	.320
In discharge	175.26 ± 52.668 (101-3190)	170.2 ± 71.033 (75-374)	.820
P^a	.577	.584	—

(Continues)

TABLE 3 (Continued)

Variables	Losartan group (n = 41)	Amlodipine group (n = 39)	P^b
Fasting blood sugar (mg/dL)			
Baseline	116.71 ± 57.067 (16-274)	120.65 ± 40.873 (72-224)	.755
In discharge	111.56 ± 33.703 (84-202)	148.15 ± 53.769 (95-252)	.059
P^a	.271	.037	—
C-reactive protein (mg/L)			
Baseline	17.97 ± 19.075 (0-50)	14.35 ± 16.94 (0-44)	.438
In discharge	19 ± 21.839 (0-50)	12.25 ± 17.261 (0-42)	.435
P^a	.483	.697	—
Erythrocyte sedimentation rate (mm/h)			
Baseline	33 ± 22.368 (2-90)	43.64 ± 31.48 (2-94)	.182
In discharge	23.44 ± 12.156 (1-40)	46.2 ± 36.622 (4-96)	.241
P^a	.320	.596	—
Lactate dehydrogenase (U/L)			
Baseline	587.21 ± 253.774 (0-1108)	585.22 ± 212.013 (264-1027)	.976
In discharge	657.37 ± 383.675 (160-1407)	529.43 ± 285.616 (256-1100)	.482
P^a	.094	.238	—
Pa O_2 (mmHg)			
Baseline	46.565 ± 23.6733 (11.9-100)	43.109 ± 20.3456 (15-86)	.576
In discharge	59.4 ± 21.6214 (31-109)	44.946 ± 22.255 (21-100)	.084
P^a	.17	.652	—
Pa Co_2 (mmHg)			
Baseline	46.522 ± 14.5597 (21.9-87.1)	40.579 ± 11.0142 (25-71)	.062
In discharge	45.66 ± 8.3316 (32-64.5)	40.711 ± 8.5917 (25-59)	.058
P^a	.90	.216	—
HCO_3 (mEq/L)			
Baseline	25.935 ± 5.6337 (16-44.3)	23.528 ± 5.1165 (13-36)	.078
In discharge	26.487 ± 4.5823 (16-35)	23.724 ± 4.6604 (16-35.8)	.058
P^a	.29	.707	—
PH			
Baseline	7.3643 ± 0.04879 (7.25-7.47)	7.3603 ± 0.05809 (7.28-7.49)	.763
In discharge	7.3642 ± 0.06536 (7.1-7.46)	7.3706 ± 0.06566 (7.23-7.49)	.745
P^a	.41	.855	—

[a]Based on paired Student's *t* tests.
[b]Based on independent *t* test.

3.4 | Drug safety

We did not found adverse effects or symptoms with the losartan and amlodipine groups that were related to these medications administration.

4 | DISCUSSION

The results of our study suggest that there were no significant difference in mortality rate, length of hospital stay, need to intubation between patients with primary HTN and COVID-19 treated with losartan and amlodipine. Moreover, all patients were achieved to targeted blood pressure.

It is a major challenge to change or continue anti-HTN medications in patients with HTN and COVID-19. A recent retrospective study found that no association between ARBs taking by patients with COVID-19 and no association between ARBs taking and poorer in-hospital outcomes.[22]

It should be considered that there was 7 years difference in the mean age of patients in the groups and it may be a notable factor in evaluating the mortality, morbidity and severity of COVID-19. Because older ages accompanying with severe presentations of COVID-19.[23]

In animal models of ARDS and SARS, recombinant ACEII can protect the body from lung injuries. In a retrospective review performed on 539 hospitalised patients suffering from an infection, it has been demonstrated that this trend continues. The risk of pneumonia and mortality rate is reduced by the in-hospital use of ACEI or ARB.[24] Moreover, according to a recent study on Japanese population, older age was an important factor to a worse prognosis in COVID-19 patients, and ACEIs/ARBs could be beneficial for the prevention of confusion in COVID-19 patients with HTN.[25]

In a study by Liu et al, it has been reported that followed by COVID-19 infection plasma angiotensin II concentration is expected to be elevated considerably.[26] However, ACEI/ARB efficacy on COVID-19-associated results has not been completely understood yet. Moreover, it is proposed that in comparison with ACEI, ARB can be more effective in the attenuation of death in patients with chronic obstructive pulmonary disease (COPD).[27,28]

Using ACEI and ARB drugs to manage hypertensive patients with COVID-19 has always been challenging. These drugs are responsible for the increase of ACEII, a cellular receptor of COVID-19 that is needed for the viral infiltration into the host.[29] Highly expression of ACE can be observed in the cell membrane of vascular endothelial cells, and more prominent it can be seen in the lungs.[30]

The correlation between ACEI/ARB pathway and the COVID-19 mortality rate may result from the co-morbidities and in-hospital medications. Previously, it has been suggested that low levels of potassium may be a marker of unopposed angiotensin II.[31,32] Thus, the link between antihypertensive drugs and coronavirus can be defined as low levels of potassium known as hypokalaemia. However, further investigations are required to approve the link between these three factors. Potassium level was reduced more significantly in patients who used losartan in the present study, also the reduction of potassium level in the amlodipine group was less than cases and not significant.

Final responses to angiotensin II in an organ can be reduced by losartan, an angiotensin II antagonist with a selective, competitive task. This drug is constantly advised for patients with high blood pressure who are afflicted to diabetic nephropathies.[33] Physiological impacts of angiotensin II such as the secretion of aldosterone are neutralised by this antihypertensive drug which can increase the activation of plasma renin because of low levels of angiotensin II.

The results of a new study show that losartan suppresses polarised Th1/Th17-mediated inflammatory responses.[34] One of the novels discovered strategies is damaging the Th1 and Th17 response results from losartan acute lung injury induced by lipopolysaccharides.

A recent study retrospective study found using amlodipine in HTN treatment in patients with COVID-19 were associated with improvement in mortality rate and critical condition of patients.[35] Therefore, amlodipine safety in COVID-19 patients was in line with our results.

The presented study has some limitations. The small sample size especially small group of patients with the critical condition and short-term follow up were the limitations of this single-centre study. Also, all of the patients were Iranian; therefore, the findings might not be generalised in different ethnicity. Possible confounding factors not otherwise accounted for this study was another limitation.

5 | CONCLUSIONS

In conclusion, there was no priority in losartan or amlodipine administration in COVID-19 patients with primary HTN. Further studies need to clarify the first-line anti-hypertension medications in COVID-19. Further studies are required to advise losartan as a safe treatment in patients with COVID-19 and primary HTN.

ACKNOWLEDGEMENT

We would like special thank to Tuberculosis and Lung Disease Research Center of Tabriz University of Medical Sciences. This work was supported by COVID-19 grant from the Tabriz University of Medical Sciences (Grant number: 65204).

DISCLOSURE

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, AS, upon reasonable request.

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How to cite this article: Nouri-Vaskeh M, Kalami N, Zand R, et al. Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hypertension: A randomised clinical trial. *Int J Clin Pract*. 2021;75:e14124. https://doi.org/10.1111/ijcp.14124