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Comparing outcomes of clonidine and captopril in patients with hypertensive urgency: A randomized clinical trial

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Original Article

Abstract

BACKGROUND: Hypertension (HTN) is the second leading risk factor for death and disability. One fourth of healthcare in Eastern Europe and Central Asia is being spent on blood pressure (BP)-related diseases. An important situation in patients with high BP is hypertensive crisis (BP > 180/120 mmHg), which is divided to hypertensive emergency and urgency. Therefore, here, we decided to compare the effect of captopril and clonidine in patients with hypertensive urgencies, and their side effects.

METHODS: This was a parallel-group randomized clinical trial. Patients, who referred to emergency ward with any symptoms of hypertensive crisis, underwent a careful history taking and clinical examination. Individuals with systolic BP (SBP) ≥ 180 mmHg or diastolic BP (DBP) ≥ 110 mmHg with no evidence of end organ damage were randomly assigned into two interventions, clonidine and captopril. 25% decrease in BP was considered as ideal relief.

RESULTS: Regarding the duration of response to treatment drugs, patients who received clonidine relieved significantly faster than those who received captopril (P = 0.016). Moreover, the frequencies of side effects such as headache, dizziness/vertigo, dry mouth, and drowsiness in the clonidine group were significantly lower than captopril group (P < 0.05).

CONCLUSION: Patients in clonidine group relieved sooner and experienced fewer side effects. Therefore, this study suggests clonidine as a more effective therapeutic for hypertensive urgency compared with captopril.

Keywords: Hypertensive Crisis; High Blood Pressure Urgency; Clonidine; Captopril

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Introduction

Hypertension (HTN), also known as high blood pressure (BP), is the subject of global public health.[1] It is one of the most prevalent non-communicable diseases (NCDs) and affects people in both developed and developing countries.[2-8] 50 million or more Americans suffer from HTN. Worldwide prevalence of HTN was estimated one billion in 2003.[9] High BP is the second leading risk factor for death and disability.[10] Nearly, 25% of healthcare in Eastern Europe and Central Asia is being spent on BP-related diseases.[10] American Heart Association (AHA) made HTN as a primary focus area of its strategic plan in the period of 2014 to 2017. The total estimated direct and indirect cost of HTN is very high all over the world. Therefore, it is important to be diagnosed in early stages and also to be controlled.[11-14]

An important situation in patients with high BP is hypertensive crisis which is characterized by a severe elevation in BP to the degree which is life-threatening (> 180/120 mmHg)[6,15,16] with or without end organ damage and requires immediate management.[16] Hypertensive emergency is accompanied by acute or ongoing end organ damage, while hypertensive urgency is not associated with any evidence of end organ damage.[6,16-18] Previous studies have implied that urgency is more prevalent. From all hypertensive crises, 76% were urgencies and 24% were emergencies.[19]

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In general, urgency HTN is managed using oral antihypertensive drugs and its initial goal is to reduce arterial pressure by no more than 25% within the first 24 hours.[15] Antihypertensive drugs are including captopril and clonidine.[6,20,21] Compared with nifedipine, captopril has less side effect.[6,20] Therefore, captopril can effectively be prescribed as an alternative to nifedipine. It is also suggested as first-line agent in hypertensive urgencies.[16] Some reported side effects for captopril are dry cough, hypotension, and renal dysfunction.[20,21] Clonidine is other pharmaceutical therapy for hypertensive urgency, which has satisfactory hypotensive effect for elevated BP.[20,22] Meta-analysis of 61 cohort studies on HTN and cardiovascular diseases (CVDs) revealed the association of systolic BP (SBP) and diastolic BP with death from ischemic heart disease (IHD) and stroke.[23] Another randomized clinical trial compared the effectiveness of clonidine and captopril to treat very high BP in postpartum women.[20] Kazerani et al. studied the effect of sublingual captopril in patients with hypertensive crisis without end organ damage, and found captopril effective for this situation.[6]

According to the literature, captopril and clonidine are two pharmaceutical therapies for hypertensive urgency and it seems that these two drugs have fewer side effects compared with nifedipine which is more common. Therefore, here, we decided to compare the effect of captopril and clonidine in patients with hypertensive urgencies, and their side effects.

Materials and Methods

This study was a double-blind randomized clinical trial that was conducted on 88 patients with hypertensive crisis who referred to Shariati Hospital of Isfahan, Iran, during 2015-2016. The protocol of current study was approved in the Islamic Azad University, Najafabad Branch, Najafabad, Iran, and current trial was approved by Iranian Registry of Clinical Trials (IRCT2015122713828n7). All participations had informed consent to enroll in the study.

All patients with urgent high BP (SBP ≥ 180 or DBP ≥ 110 mmHg) were included into study. Besides, exclusion criteria included: (1) any evidence of harmful side effect such as hypersensitivity to drugs or anaphylactic shock or other life-threatening problems, (2) pregnancy, and (3) refusing to continue the study.

First, patients who referred to emergency ward and had some symptoms including headache, dizziness, epistaxis, weakness, high BP (measured at home), blurred vision, dyspnea, nausea, and vomiting underwent a careful history taking and clinical examination by a clinician. SBP and DBP of each patient was measured by use of mercury sphygmomanometer (Erkameter 3000, Germany), two times while they lay down on back, by trained nurses. Individuals with SBP ≥ 180 mmHg or DBP ≥ 110 mmHg in first measurement rested for five minutes and after this time, the BP was measured again.

After diagnosis of patients based on clinical and physical examination and based on inclusion criteria, they were enrolled into study. The patients were divided randomly into two parallel groups as clonidine and captopril by random allocation software using blocking method. The patients, physician, data collector, and data analyzer were not aware of group type (clonidine or captopril) and groups were named as A and B; thus, double-blind design was done. Drugs were named A and B, respectively, and patients, doctors, and researchers were not aware of drugs' name. The shape of drugs was similar and they were coded by A and B groups; the drugs were created in the pharmaceutical laboratory of Isfahan University of Medical Sciences.

Data of patients including age, sex, risk factors such as obesity, smoking, hyperlipidemia, diabetes mellitus (DM), baseline SBP and DBP, time to ideal relief (duration of received drugs to relief symptoms), drug side effects, causes of BP elevation (noting use of drugs, changing diet, unhealthy diet such as diets with high salt), and stress [based on the Depression, Anxiety and Stress Scale-21 Items (DASS-21)] were completed during the study.

First group received sublingual captopril 25 mg, and they were asked not to drink or swallow until dissolving the drug. Second group received oral clonidine 0.1-0.2 mg, followed by 0.05-0.1 mg every 1 to 2 hours, to the maximum dose of 0.6-0.7 mg. BP was measured every 15 minutes until 150 minutes after using the prescribed drug and patient received the next dose if the BP did not reduce. 25% decrease in BP was considered as acceptable response to drug or ideal relief. All patients were monitored and observed under supervision of physician for drug side effects such as headache, palpitation, dizziness/vertigo, dry mouth, and drowsiness during 2 hours in emergency ward. Researchers evaluated causes of aggravation of HTN as possible.

If the BP did not decrease after an hour, patients received additional dose of intervention drug. Time to ideal relief was considered as the duration

between receiving the intervention therapy until the BP decreased to 25% of pretreatment BP, and was measured and recorded in minute.

Statistical analysis: The sample size was calculated from Cochran's formula in which the type one error was preserved at 0.05, and the test power was 80%. The sample size for each group was 44. The convenience sampling method was applied. Eighty-eight patients who were diagnosed as urgent high BP and met inclusion criteria were recruited in this study and randomly assigned into two intervention groups, clonidine or captopril. Figure 1 shows the flow diagram of participants.

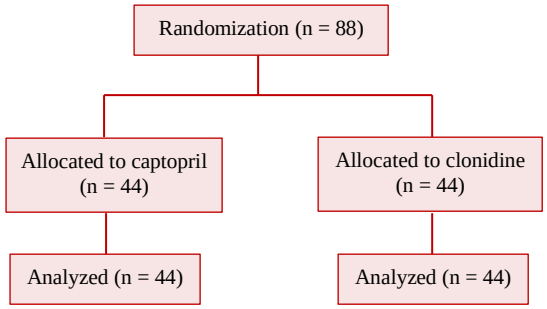

Figure 1. Flowchart diagram of participation in study

Information was registered in and analyzed by SPSS software (version 22, IBM Corporation, Armonk, NY, USA). The quantitative variables were shown as mean and standard deviation (SD) and the qualitative variables were shown as frequency and percent. Independent t-test was used to compare quantitative variables between groups and chi-square test and Fisher's exact test were used to compare qualitative variables between two groups. Significance level was considered as $P < 0.05$.

Results

All 88 participants completed the study. The youngest and the oldest participants were 34 and 91 years old. Mean ± SD of age was 63.0 ± 13.2 and 68.0 ± 11.8 years in clonidine and captopril groups, respectively. Mean age was normally distributed (P = 0.849) and did not differ significantly between two groups (P = 0.064).

39 (44.3%) participants were men and 49 (55.7%) were women. 40.9% of patients in clonidine and 47.7% of patients in captopril groups were men. Therefore, sex proportion did not differ significantly between two groups (P = 0.520).

Participants were studied for HTN risk factors and the causes of hypertensive crisis. Results are summarized in table 1. There was no significant difference between two groups based on risk factors and hypertensive crisis causes (P > 0.05).

Hyperlipidemia was the most frequent accompanied risk factor. Not using antihypertensive drugs in patients with already diagnosed high BP was the most frequent cause for hypertensive crisis.

The mean ± SD of SBP and DBP were 189.3 ± 17.8, 105.4 ± 13.3 and 185.1 ± 23.5, 95.5 ± 14.1 mmHg in clonidine and captopril groups at base time, respectively. The difference was not significant between two groups (P = 0.348).

Table 1. Relationship of risk factors between captopril and clonidine groups

		Captopril	Clonidine	P
Risk factors	Obesity (BMI ≥ 30 kg/m^2)	9 (20.5)	9 (20.5)	> 0.999*
	Smoking	6 (13.6)	6 (13.6)	> 0.999*
	Hyperlipidemia	28 (63.6)	21 (47.7)	0.133*
	DM	15 (34.1)	16 (36.4)	0.823*
	Age (year)	64.8 ± 11.1	61.4 ± 14.4	0.070**
	Sex			
	Women	23 (52.3)	26 (59.1)	0.520*
	Men	21 (47.7)	18 (40.9)	
Hypertensive crisis causes	Not using antihypertensive drugs	29 (65.9)	24 (54.5)	0.276*
	New hypertension case	8 (18.2)	6 (13.6)	0.560*
	Stress***	13 (29.5)	14 (31.8)	0.817*
	Unhealthy diet****	1 (2.3)	3 (6.8)	0.306*

Data are presented as mean ± standard deviation (SD) or number and percentage
*Fisher's exact test;**Independent t-test; ***In Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), disorders which are precipitated by specific stressful and potentially traumatic events are included in a new diagnostic category, "Trauma and Stress-Related Disorders," which includes both Adjustment Disorders (ADs) and post-traumatic stress disorder (PTSD); ****Unhealthy diet includes overeating of fatty and greasy food, milky products, sweet foods, highly flavored food, too pungent food, as well as drinking too much alcohol, leading to the formation of Damp-Heat syndrome
BMI: Body mass index; DM: Diabetes mellitus

The mean and SD of time to relief for patients is presented in table 2. According to the results of this table, patients who received clonidine relieved significantly sooner than those who received captopril (P = 0.016).

Table 2. Time to relief (minute) based on groups

	Time to relief (minute) (mean ± SD)	P
Clonidine (n = 44)	45.9 ± 30.1	0.016*
Captopril (n = 44)	64.0 ± 38.7	

SD: Standard deviation

The mean difference of time to relief between men and women was not statistically significant in patients, neither in clonidine (P = 0.524) nor in captopril (P = 0.884) group.

The two interventions were compared for side effects. Observed side effects and the result of statistical tests are presented in table 3.

Table 3. Complication of medications based on groups

	Clonidine [n (%)]	Captopril [n (%)]	P**
Dry mouth	1 (2.3)	8 (18.2)	0.014*
Drowsiness	0 (0)	6 (13.6)	0.011*
Headache	21 (47.7)	33 (75.0)	0.009*
Dizziness/vertigo	20 (45.5)	31 (70.5)	0.018*
Palpitation	6 (13.6)	4 (9.1)	0.502

*P-value < 0.05 was considered as statistical significance; **Fisher's exact test was applied

Headache and dizziness were the most frequent side effects in both groups. Patients in clonidine group experienced significantly less side effects including dry mouth, drowsiness, headache, and dizziness (P < 0.05). Although the patients in clonidine group experienced more palpitation than those in captopril group, the difference was not statistically significant (P = 0.502). No individual experienced angioedema, cough, and rebound HTN.

Discussion

Based on our results, in the patients with hypertensive urgency, using clonidine was better than captopril, because using clonidine had faster effect than captopril and also the frequency of side effects such as headache, dizziness/vertigo, dry mouth, and drowsiness in the clonidine group was significantly lower than captopril group.

HTN is one of the most prevalent NCDs all over the world. The previous studies have estimated the prevalence of HTN as 29.8% in India[24] and 23% to 33% in African adults.[3,25] An important situation in patients with HTN is hypertensive crisis which is divided into emergency and urgency HTN.[15,16] Hypertensive urgency is more prevalent and can be managed using oral antihypertensive drugs.[15,19]

Based on our results, frequency of hypertensive urgency in women was more common than men. This result was similar to previous studies by Unger et al.[5] and Zampaglione et al.,[19] in which the hypertensive crisis was more prevalent in women. In a study by Kazerani et al., the prevalence of hypertensive urgency was higher in women rather than men.[6]

Besides this finding, there is some evidence that the prevalence of HTN is higher in women than men around the world.[4,5] In Iran, a study on university students reported higher prevalence of high BP in men rather than women. In this study, the population was somehow different and subjects were selected from young adults.[26] Other study in China showed that men had higher prevalence of pre-HTN, but women had higher prevalence of HTN.[27] This evidence suggests that the higher prevalence of hypertensive urgency in women may be due to higher prevalence of HTN in women.

In our study, hyperlipidemia and DM were the two most prevalent accompanied risk factors of HTN. The previous study also reported both hyperlipidemia and DM as two important accompanied risk factors of HTN.[14]

Nifedipine was one of the most common therapeutics for hypertensive urgency. However, its rapid decrease in BP may increase the risk of heart attack and central nervous system (CNS) injury.[6,17] In a study by Maleki et al., captopril and nifedipine had the same effect on BP reduction; however, captopril had lower side effects.[21]

In our study, the most prevalent side effects were headache and dizziness in both clonidine and captopril groups. However, the prevalence of both side effects was significantly higher in captopril group. Other side effects included dry mouth, drowsiness, and palpitation. Except for palpitation, the prevalence of two other side effects was significantly higher in captopril group. In a previous study, captopril side effects were reported as dry cough, hypotension, and decreased renal function.[20] In our study, no individual experienced angioedema, cough, and rebound HTN.

Vaidya and Ouellette in 2007 reported the same onset of action for clonidine and captopril which begins within 15 to 30 minutes. According to their study, the maximum drop in BP occurs sooner in captopril.[15] However, in our study, time to ideal

relief (25% of pretreatment BP) was significantly shorter in clonidine group. In a study by Kazerani et al., the ideal SBP and DBP reduction (25% of initial BP) was detected in 68.4% and 65.3% of patients, respectively, 30 minutes after receiving sublingual captopril. After 60 minutes, the ideal decrease was reported in 53.5% of patients.[6] In other study, captopril ideally reduced BP by 27.6% in 60 minutes.[21] There was no statistically significant difference of time to ideal relief between men and women, neither in clonidine nor in captopril. There was a limited body of published literature comparing the effect of clonidine and captopril on time to ideal relief.

The limitations of our study were low sample size, not following up patients in long term, and not evaluating other effective variables in hypertensive crisis.

Conclusion

According to our results, hyperlipidemia and DM were the most prevalent accompanied risk factors of hypertensive urgency. Clonidine and captopril, both, are effective in hypertensive urgency. But, time to ideal relief was significantly lower in clonidine group. There was no significant difference in time of relief between men and women in both groups. On the other hand, patients in clonidine group experienced significantly fewer side effects although in this group, women showed more headache and dizziness than men.

Therefore, management by clonidine is more effective with less drug side effects strategy in hypertensive urgency.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

Conception or design of the work: AM, RA, AK
Data collection: AK, RA, AM
Data analysis and interpretation: RA, AK, AM
Drafting the article: RA, AM, AK
Critical revision of the article: AM, RA
Final approval of the version to be published: AM, RA

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