Iran Red Crescent Med J. 2018 June; 20(6):e61606. doi: 10.5812/ircmj.61606.

Published online 2018 May 27. **Research Article**

Sublingual Versus Oral Captopril for Decreasing Blood Pressure in Hypertension Urgency: A Randomized Clinical Trial

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Received 2017 September 11; **Revised** 2017 December 06; **Accepted** 2017 December 21.

Abstract

Background: Captopril, a short-acting antihypertensive agent, is widely used in case of emergency to control blood pressure. Although sublingual Captopril has a faster onset of action, it is less tolerated.

Objectives: This study aimed to evaluate the efficacy, side effects, and tolerability of sublingual versus oral captopril in an emergency setting.

Methods: Hypertensive patients, without acute target organ damage were randomly administered 25 mg Captopril sublingually or orally (35 patients in each group) using block randomization. Blood pressure was measured at 0, 10, 20, 30, 45, 60, and 120 minutes after the administration. Patient satisfaction was subjectively scored on a scale of 1 - 10, and any side effect was recorded (Iranian registered clinical trials # IRCT2015110924963N1).

Results: The mean age of the study groups was 59.61 $\pm$ 9.34 years. Systolic and mean blood pressure significantly decreased after 10, 20, and 30 minutes of sublingual administration ($P < 0.05$), but diastolic blood pressure did not decrease. This difference in the blood pressure reducing effect decreased by 60 and 90 minutes and almost equalized after 90 minutes. Headache was observed as a side effect in two patients in the sublingual group. The convenience and satisfaction scores were much lower in the sublingual group (median of 6 (25th percentile: 6, 75th percentile: 7) in sublingual group versus median of 10 (9, 10) in Captopril group, $P < 0.001$).

Conclusions: In our study, the systolic and mean blood pressure decreased more rapidly in the sublingual Captopril group than in the oral Captopril group in the first 30 minutes after administration. Patients better tolerated the oral preparation, and the difference in the blood pressure reducing effect between the groups almost equalized after 90 minutes.

Keywords: Administration, Captopril, Hypertension, Oral, Sublingual, Urgency

1. Background

Hypertension, "the silent killer," is a controllable risk factor and is considered a major cause of mortality worldwide (1, 2). Hypertensive emergency or crisis, which requires immediate blood pressure (BP) reduction with intravenous medication and intra-arterial monitoring in an intensive care unit (3, 4), is defined as a sudden increase in BP (usually $\geq$ 220/130 mm) along with acute target organ damage (to the central nervous system, heart, kidney, retina, or blood vessels) (3). Conversely, severely elevated BP in the absence of acute target organ damage is considered as hypertensive urgency (3-6). In this setting, even in patients with BP as high as 220/130 mmHg, a rapid reduction in BP has no proven benefit (3, 4, 7), and gradual reduction over 24 - 48 hours (6, 7) with a short-acting oral medication is recommended (3). For many years, sublingual or oral short-acting nifedipine had been used for this purpose; however, considering the serious ischemic outcomes that have been reported, which may be due to a rapid and uncontrolled fall in BP, this drug has been prohibited for use (6).

Currently, angiotensin-converting enzyme inhibitors (ACEIs) are among the recommended first-line therapy for the treatment of hypertension (2, 3, 8). Captopril is an ACEI that has been administered orally and sublingually in hypertension urgencies (7, 9-23). It exhibits peak effect 1 - 2 hours after oral administration (24). Sublingual Captopril in comparison to oral Captopril causes an earlier increase in plasma Captopril concentration (25) and may decrease BP faster (10, 15, 19). The reduction in BP by sublin-

gual Captopril starts within 10 minutes of administration and peaks after 30 minutes (10, 16, 19, 26), which is slower than that by Nifedipine (19). However, this difference in the effect of sublingual versus oral intake may equalize after 60 minutes (10). Furthermore, the bitter taste of sublingual Captopril may bother patients (7) and cause a chemical burn in the oral mucosa as well as hypersensitivity (6).

2. Objectives

After the use of Nifedipine was condemned (6), sublingual Captopril has been widely used to control severe hypertension in hypertensive urgencies. However, tolerance to sublingual administration is not as good as oral administration (7), and it is unclear whether there are any additional benefits with sublingual administration. Therefore, this study was performed to evaluate the efficacy, possible side effects, and patient satisfaction of sublingual versus oral Captopril.

3. Methods

In this randomized clinical trial, patients admitted to the emergency department of two hospitals in Shahroud, Iran, during the years of 2015 and 2016, were included in the study. The two hospitals "Emam Hossein Hospital (governmental), and Khatam Al-Anbia (private)" are the only two centers with cardiac care unit and are referral for heart diseases in the city.

Patients with previously diagnosed (BP $\geq$ 160/90 mmHg) or new-onset severe hypertension (BP $\geq$ 180/110 mmHg) but without target organ damage (hypertension urgency), were included in this study. BP was measured at least twice in the sitting position with at least 5-minutes intervals. Patients requiring intravenous medication for BP control or another antihypertensive drug for a different reason, on high dose of ACEIs or ARBs before admission (> 50 mg/d Captopril, > 10 mg/d Enalapril, > 5 g/d Lisinopril, > 50 mg/d Losartan, > 80 mg/d Valsartan), and who suffered myocardial infarction with acute chest pain at presentation, severe renal or hepatic failure, papillary edema, pulmonary edema, loss of consciousness, seizure, aortic dissection, or bilateral renal artery stenosis; pregnant patients, patients with a history of overt allergy or angioedema with ACEIs; and patients unwilling to sign a written consent were excluded. Among the included patients who were considered for the study, 17 were excluded as they were unwilling to participate in the study and three were excluded for other reasons (Figure 1).

3.1. Interventions and Randomization

Using block randomization, seventy patients were randomly allocated to receive 25 mg sublingual (SL group) or oral (OR group) Captopril tablets (Captopril® 25 mg, Exir Pharmaceutical co. Iran; 35 patients in each group).

3.2. Measurements

Systolic and diastolic BP (SBP and DBP, respectively) were measured at 10, 20, 30, 45, 60, 90, and 120 minutes after administration by a single experienced blinded observer with a calibrated aneroid sphygmomanometer (minimus® II Sphygmomanometers, Riester, Germany). Mean BP (MBP) was calculated at different time points as follows: MBP = (2DBP + SBP)/3). Heart rates (HR) were also measured by the investigator by counting the pulse rate. The patients were asked whether they were experiencing any discomfort, including headache, dizziness, nausea, vomiting, muscle cramps, abdominal pain, indigestion, dry mouth, cough, flushing, urticaria, skin rashes, or bitter taste. At the end of BP measurement, the patients were asked to score their satisfaction with the route of administration compared with their previous experience on a scale of 1-10. Basic characteristics and all other data were recorded in a checklist.

3.3. Outcome

The primary outcome of the study was the decrease in SBP at 30 minutes. The secondary endpoints included SBP, DBP, MBP, and HR changes at 10, 20, 45, 60, 90, and 120 minutes and MBP, DBP, and HR changes at 30 minutes.

3.4. Treatments and Ethical Considerations

Besides treatment of hypertension by oral or sublingual Captopril, if BP was not under control after 120 minutes, the emergency department physician decided about other possible treatments independently.

The study was conducted as part of a thesis under the medical doctor program at the Islamic Azad University. The local Ethical committee at Islamic Azad University approved the study protocol, and the Ethical guidelines of the 1975 Declaration of Helsinki were considered. Written signed consents were obtained after explaining the trial to the patients. The study protocol has been registered at Iranian registry of clinical trials (#IRCT2015110924963N1).

3.5. Sample Size and Statistical Analysis

The sample size was calculated based on a pilot study of 10 patients. With an α error of 0.05 and power of 80%, assuming 24.7 $\pm$ 8.5 mmHg and 19 $\pm$ 8.3 mmHg reductions in blood pressure of SL and OR groups respectively (a mean

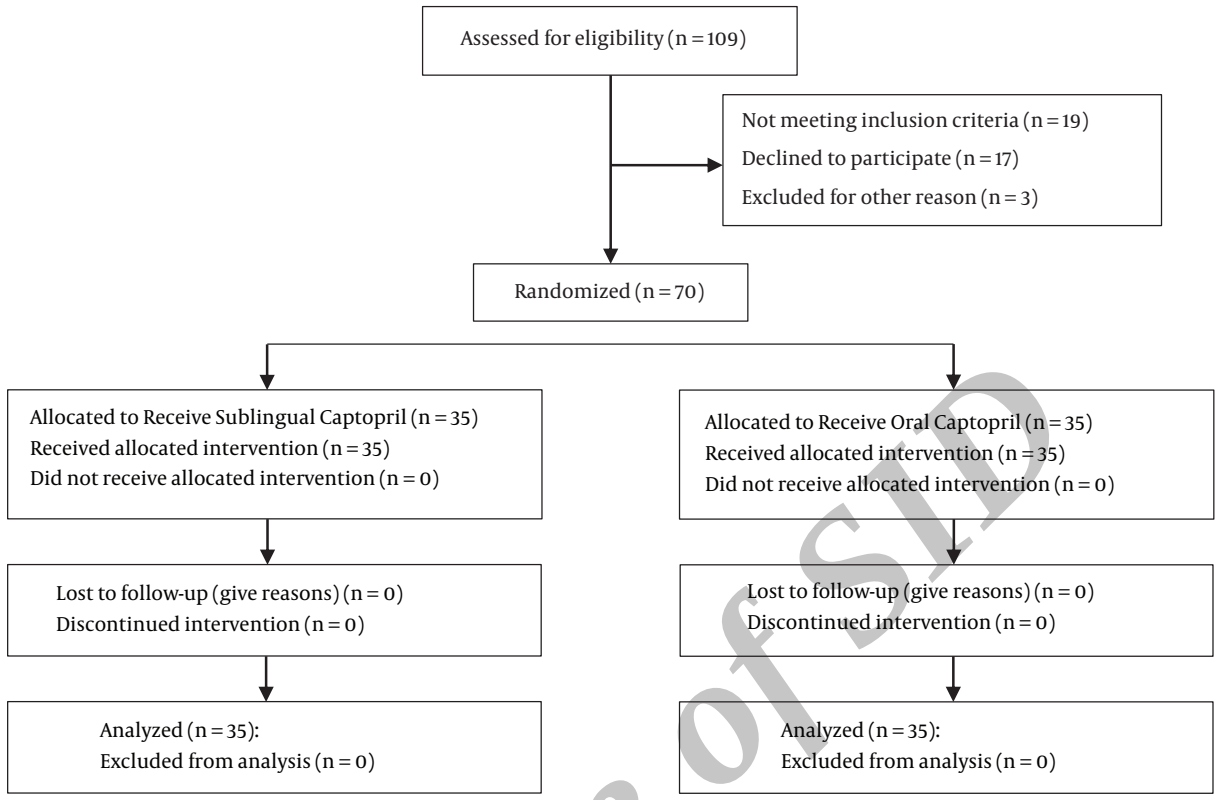

Figure 1. Flow diagram of the enrolment, intervention allocation, follow-up, and data analysis

difference in decrease of SBP of approximately 5.7), we concluded that we would need 35 patients in each group.

Statistical analysis was performed using the statistical software SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL., USA)) and per protocol analysis was done. The data are presented as mean ± standard deviation for numerical variables with a normal distribution or as medians (25 percentile, 75 percentile) for variables without a normal distribution. Categorical variables are represented as numbers and percentages. Numerical variables were tested for normal distribution by the one-sample Kolmogorov-Smirnov test, Shapiro-Wilk test (for < 50 samples), and histograms. For comparison of changes in BP in the SR and OR groups, independent sample t-test (if it showed a normal distribution) or Mann-Whitney, non-parametric test (if did not have normal distribution) was considered. For evaluation of the changes in two related samples, paired t-test or non-parametric Wilcoxon Signed Ranks (when needed) was performed. Repeated measure analysis was performed to evaluate the difference of SBP, DBP, and MBP between different time intervals. The categorical variables were compared using the Pearson Chi-square or the Fisher exact test, as required. P values of ≤ 0.05 indicated statistical significance.

4. Results

The basic characteristics of the two groups are presented in Table 1.

Repeated measure analysis using the Bonferroni method adjustment revealed that SBP and MBP showed a significant ($P < 0.05$) decline after administration of Captopril at all time-intervals excluding 90 to 120 minute. The decrease in DBP was significant ($P < 0.05$) except baseline to 10 minutes, 60 to 90 and 90 to 120 minutes.

A comparison of decrease in SBP, DBP, MBP, and HR in the SL and OR groups at different time intervals after drug intake is provided in Table 2. A repeated measures analysis with a Greenhouse- Geisser correction determined that mean SBP differed statistically significantly between the time points considering the synchronous and interactive effect of the time and method of the Captopril usage. ($F = 2.977$, $P = 0.019$, Figure 2A); however, this measurement was insignificant between different DBPs ($F = 0.716$, $P = 0.573$, Figure 2B) and MBPs ($F = 1.009$, $P = 0.402$, Figure 2B).

Table 1. Basic Charactristics of Sublingual (SL) and Oral (OR) Captopril Group

Variables	SL Captopril	OR Captopril	P Value
Age, y	58.14 ± 9.11	61.12 ± 9.47	0.188
Sex (female), No. (%)	25 (71.4)	26 (74.3)	0.788
BMI, kg/m^2	28.21 ± 3.15	28.38 ± 2.10	0.784
New HTN, No. (%)	6 (17.1)	5 (14.7)	0.782
Duration of HTN, mo	96 (22, 126)	36 (12, 127)	0.312
Under Tx with Captopril, No. (%)	6 (17.1)	7 (20.0)	0.759
Under Tx with ARBs, No. (%)	13 (43.3)	15 (48.4)	0.692
Under Tx with ASA, No. (%)	5 (14.3)	4 (11.4)	0.500
Hx of cigarrete smoking, No. (%)	3 (8.6)	3 (8.6)	0.663
Hx of DM, No. (%)	7 (20)	6 (17.1)	0.759
Hx of Proven IHD, No. (%)	2 (5.7)	2 (5.7)	0.693
Basal SBP, mmHg	170 (165, 180)	170 (160, 180)	0.315
Basal DBP, mmHg	100 (90, 110)	95 (90, 100)	0.172
Basal MBP, mmHg	123 (117, 128)	120 (117, 127)	0.151
Basal HR, Beat/minute	74.97 ± 9.56	76.63 ± 11.03	0.504

Abbreviations: ACEIs, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; ASA, Acetylsalicylic Acid (Aspirin) BMI, Body Mass Index; DBP, Diastolic Blood Pressure; DM, Diabetes Melitus; HR, Heart Rate; HTN, Hypertension; Hx, History; IHD, Ischemic Heart Disease; MBP, Mean Blood Pressure; SBP, Systolic Blood Pressure; Tx, Treatment.

At baseline, the mean HR in the groups was 75.80 ± 10.28, which marginally increased to 77.49 ± 7.65 after 120 minutes (P = 0.272). Figure 3 shows the trend of changes in HR in the two groups. The mean HR showed a minimal increase from 74.97 ± 9.56 to 76.52 ± 7.95 beats/min in the SL group (P = 0.314) and from 76.63 ± 11.03 to 78.44 ± 7.34 beats/min (P = 0.255) in the OR group after 120 minutes.

Side effects (headache) were observed only in two patients (3%) of the SL group. The mean scores for patient satisfaction were 7.94 out of 10 (8.0 (6.0, 10.0)). These scores were significantly higher in the OR group than in the SL group (6 (6, 7), mean = 6.40 in SL versus 10 (9, 10), mean = 9.49 in the Captopril group, P < 0.001). The highest score in the SL group was 8.

5. Discussion

It is possible that sublingual Captopril may have a faster onset of action than that of oral Captopril (7, 10, 14, 15, 19, 24, 25), which may be helpful in an emergency setting. Sublingual Nifedipine may have been replaced by sublingual Captopril, because of the slower onset of action (13, 19, 21) and similar efficacy (12, 21, 26). The results of our study confirmed that sublingual Captopril decreased SBP and MBP significantly more rapidly than oral Captopril at 10, 20, 30 minutes (Table 2 and Figure 2A - C). On the other hand, the decrease in DBP was not statistically significant. The reduction in SBP, DBP, and MBP continued for 120 minutes; however, the decrease in blood pressures, almost equalized in the two SL and OR groups after 90 minutes.

Most (10, 14, 15, 19, 25) but not all (7) studies have shown a more rapid antihypertensive effect with the sublingual route than the oral route, which equalizes after 60 minutes (10). Karakilic et al. did not report any significant reduction in BP after sublingual administration compared to oral administration of Captopril; however, about 91.5% of their patients were under treatment with antihypertensive medications, including 63.5% consuming ACEIs (7). Conversely, we excluded those who were under treatment with high-dose ACEIs or ARBs. Furthermore, we randomized our patients to prevent possible biases. Evaluating the clinical effect of medication, we did not measure the blood levels of the drug. Hence, sooner action of the sublingual prescription according to our finding was a clinical response and not confirmed by the laboratory.

In many studies, a decrease (12, 18, 20) or no change in HR after sublingual Captopril intake was observed (13) (the reason underlying increased fatal ischemic outcomes with Nifedipine intake (6)). Our study also did not show any significant increase in HR after sublingual or oral Captopril intake.

Most patients in our study did not complain of any complication (97%). Most of the studies performed on the

Table 2. A Comparison of Decrease in Systolic Diastolic and Mean Blood Pressures and Heart Rate, in the Sublingual (SL) and Oral (OR) Captopril Groups at Different Time Intervals

	Decrease SBP, SL Captopril	Decrease SBP, OR Captopril	P Value	Decrease DBP, SL Captopril	Decrease DBP, OR Captopril	P Value
10 min, mmHg	15 (10, 20)	6 (0.0, 10)	0.003	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.086
10 min, %	8.84 (5.56, 12.90)	3.65 (0.00, 6.67)	0.004	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.089
20 min, mmHg	20 (10, 25)	10 (10, 20)	0.006	0.0 (0.0, 10.0)	0.0 (0.0, 5.00)	0.121
20 min, %	10.53 (6.25, 13.51)	6.25 (5.26, 10.00)	0.007	0.0 (0.0, 9.55)	0.0 (0.0, 4.76)	0.182
30 min, mmHg	20 (20, 30)	20 (13, 25)	0.010	10 (0.00, 10.0)	5.0 (0.0, 10.0)	0.306
30 min, %	12.5 (10.53, 17.65)	10.53 (7.98, 15.00)	0.012	9.09 (0.0, 11.11)	4.76 (0.0, 10.0)	0.429
45 min, mmHg	25 (20, 30)	20 (15, 27)	0.039	10.0 (5.0, 10.0)	10.0 (0.0, 10.0)	0.438
45 min, %	14.56 ± 4.27	12.33 ± 4.92	0.046	10.0 (4.88, 11.11)	10.0 (0.0, 11.11)	0.435
60 min, mmHg	30 (25, 35)	27 (20, 33)	0.227	10.0 (10.0, 15.0)	10.0 (10.0, 15.0)	0.622
60 min, %	16.61 ± 4.87	15.35 ± 5.35	0.307	11.11 (10.0, 15.48)	11.11 (10.0, 15.79)	0.799
90 min, mmHg	30 (25, 40)	30 (25, 37)	0.326	10.0 (10.0, 20.0)	10.0 (10.0, 15.0)	0.162
90 min, %	18.18 ± 4.59	17.44 ± 4.41	0.496	11.11 (10.0, 20.0)	11.11 (10.0, 16.67)	0.216
120 min, mmHg	32 (25, 40)	31 (26.3, 40)	0.995	10.0 (10.0, 20.0)	10.0 (10.0, 20.0)	0.287
120 min, %	18.53 ± 4.42	18.57 ± 4.09	0.972	11.11 (10.0, 20.87)	11.11 (10.0, 20.0)	0.385
	Decrease MBP, SL Captopril	**Decrease MBP, OR Captopril**	**P Value**	**HR changes, SL Captopril**	**HR changes, OR Captopril**	**P Value**
10 min, mmHg	6.67 (3.33, 6.67)	3.33 (0.0, 3.83)	0.003	0.0 (-4.0, 0.0)	0.0 (0.0, 0.0)	0.066
10 min, %	4.88 (2.70, 5.88)	2.70 (0.0, 3.24)	0.005	0.00 (-5.00, 0.00)	0.0 (0.00, 0.00)	0.063
20 min, mmHg	8.63 ± 4.51	5.60 ± 4.04	0.011	-2.0 (-4.0, 4.0)	0.0 (-4.0, 4.0)	0.79
20 min, %	6.97 ± 3.63	4.59 ± 3.32	0.014	-2.70 (-5.56, 4.55)	0.0 (-5.4, 3.0)	0.697
30 min, mmHg	12.33 ± 4.73	9.64 ± 4.45	0.034	-4.0 (-4.0, 4.0)	-2.0, (-4.0, 2.0)	0.957
30 min, %	9.98 ± 3.86	7.94 ± 3.67	0.049	-5.13 (-5.88, 4.76)	-2.70 (-5.56, 3.03)	0.800
45 min, mmHg	14.0 (10.0, 16.67)	13.33 (10.0, 16.67)	0.281	-2.0 (-4.0, 4.0)	-2.0 (-4.0, 4.0)	0.812
45 min, %	11.58 ± 3.41	10.15 ± 3.95	0.152	-3.13 (-6.67, 4.35)	-2.78 (-5.88, 2.63)	0.702
60 min, mmHg	16.67 (15.0, 20.0)	16.67 (14.17, 20.0)	0.841	-4.0 (-6.0, 4.0)	-4.0 (-6.0, 2.0)	0.867
60 min, %	14.38 ± 3.35	13.81 ± 4.53	0.591	-5.41 (-9.09, 4.55)	-5.13 (-8.33, 3.03)	9.86
90 min, mmHg	20.09 ± 5.02	18.03 ± 5.44	0.147	-4.0 (-6.0, 4.0)	-4.0 (-6.0, 4.0)	0.634
90 min%	16.26 ± 3.87	14.85 ± 4.34	0.204	-5.56 (-9.68, 5.00)	-5.56 (-8.33, 4.65)	0.879
120 min, mmHg	20.33 ± 4.94	19.17 ± 5.33	0.421	-4.0 (-8.0, 4.0)	-4.0 (-6.0, 4.0)	0.895
120 min, %	16.47 ± 3.74	15.77 ± 4.29	0.542	-5.56 (-10.0, 4.76)	-5.41 (-7.69, 4.73)	0.747

Abbreviation: DBP, Diastolic Blood Pressure; HR, Heart Rate; MBP, Mean Blood Pressure; min, Minute; OR, Oral; SBP, Systolic Blood Pressure, SL, Sublingual.

use of Captopril in hypertension emergency have also not found any important side effects (11, 13, 18). There have been only a few reports of headache, nausea, and vomiting (7). In our study, only two patients in the SL Captopril group complained of headache. However, whether headache is more prevalent with sublingual Captopril than with oral Captopril, remains to be investigated in further studies.

Our patients reported significantly lesser satisfaction with sublingual intake of Captopril than with oral intake ($P < 0.001$). None of the patients in the SL group were completely satisfied with the route of drug intake (the maximum score was 8), whereas more than half of the patients in the OR group were fully satisfied (half had score of 10). The bitter taste of sublingual Captopril may be the reason for their displeasure (7). Furthermore sublingual prescription can cause chemical burns in the oral mucosa as well as hypersensitivity (6). This novel finding in our study, in the absence of clear benefit of early onset of the action of the

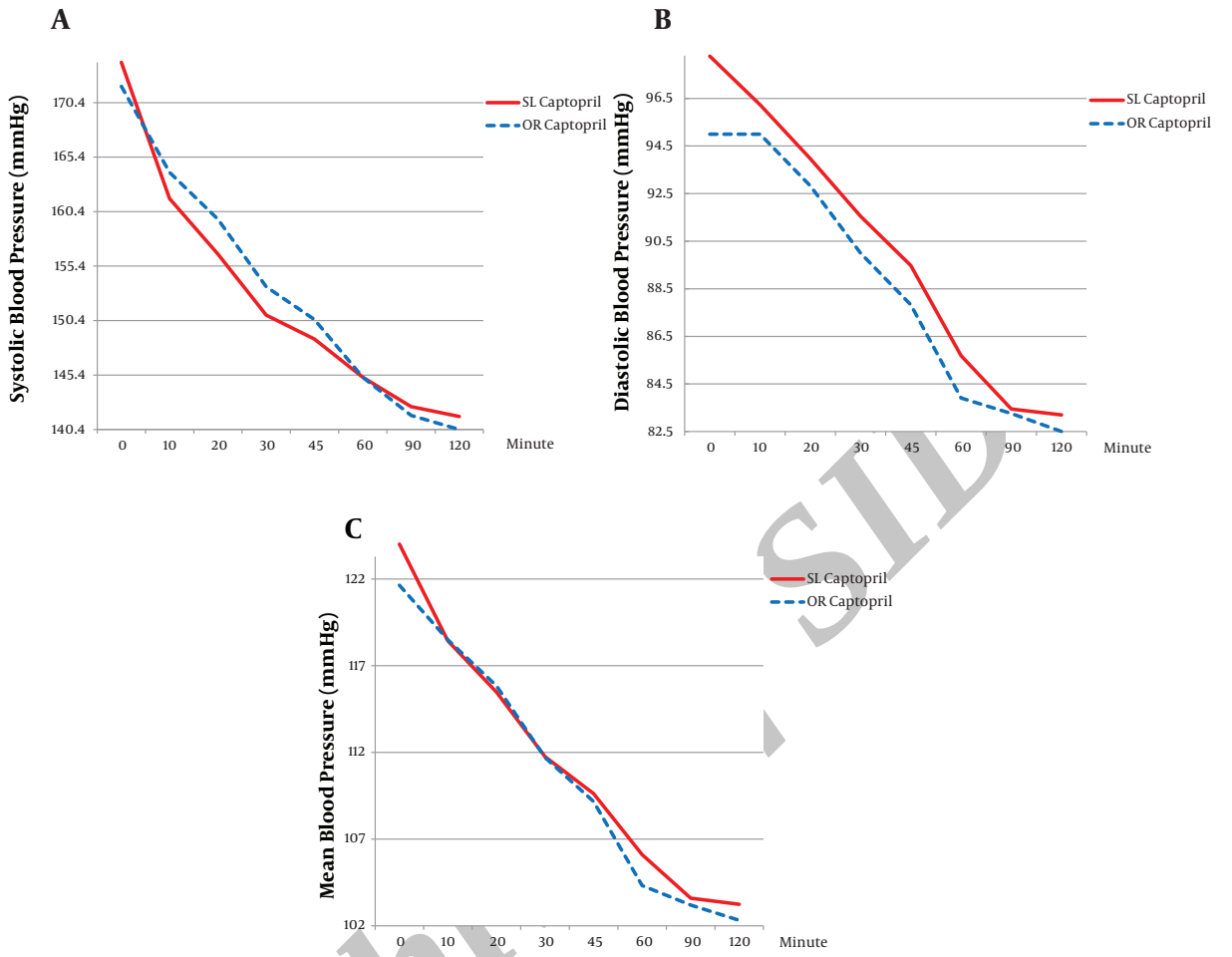

Figure 2. The pattern of decrease in blood pressure measured as mmHg (vertical axis) in different time intervals after sublingual (SL) Captopril and oral (OR) Captopril intake. A, Systolic blood pressure (SBP); B, Diastolic blood pressure (DBP); C, Mean blood pressure (MBP).

drug and equalization of the effect after 90 minutes, may have important clinical implications and could be considered by the physicians for the choice of route of Captopril administration.

5.1. Conclusion

Our study showed that in hypertensive patients without acute target organ damage, sublingual Captopril can decrease SBP and MBP but not DBP more rapidly than oral captopril in the first 30 minutes after intake. The change in heart rate was minimal after sublingual and oral administration and a few side effects were observed. However, patients were significantly more satisfied with oral administration of Captopril and tolerated it better. Furthermore, the difference in the BP reducing effect almost equalized after 90 minutes. When a faster onset of action is desired, sublingual administration of Captopril, irrespective of its bitter taste and dissatisfaction among patients could be considered.

Acknowledgments

We thank the physicians, nurses, and other personnel of the emergency department of Khatam Al-Anbia and Emam Hossein Hospitals in Shahroud who assisted us in recruiting patients. We also thank Miss Masoumeh Rezazadeh for Article review and helping us improve the manuscript. Finally, we wish to acknowledge the great help and support provided by Clinical Research and Development Unit, Shahid Rajaei Educational and Medical Center, Alborz University of Medical Sciences.

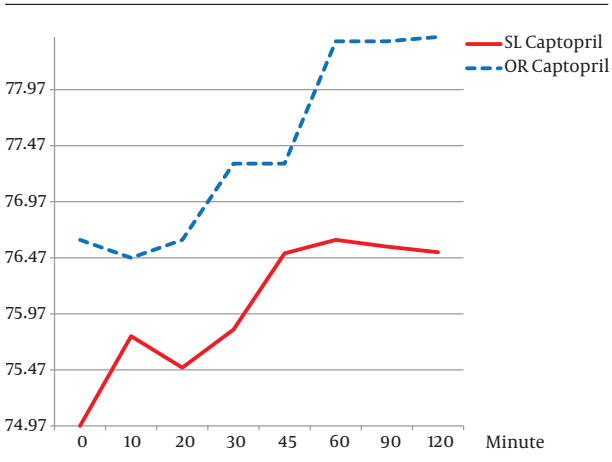

Figure 3. The pattern of mean heart rate changes (beat/minute, vertical axis) in different time intervals after sublingual (SL) Captopril and oral (OR) Captopril intake

Footnotes

Authors' Contribution: Study concept and design, Mehdi Mousavi, Nasrin Razavianzadeh, Mania Armin; acquisition of data, Mania Armin; analysis and interpretation of data, Mehdi Mousavi, Maryam Fadaei Dashti; drafting of the manuscript, Mehdi Mousavi, Nasrin Razavianzadeh, Mania Armin; critical revision of the manuscript for important intellectual content, Mehdi Mousavi, Nasrin Razavianzadeh, Mania Armin, Maryam Fadaei Dashti; statistical analysis, Mehdi Mousavi; administrative, technical, and material support, Nasrin Razavianzadeh; study supervision, Mehdi Mousavi, Nasrin Razavianzadeh.

Financial Disclosure: The authors have no financial disclosures and conflicts of interest related to study to declare. This study was performed as a part of a thesis for the Medical Doctor degree of Dr. Mania Armin according to the rules of the Islamic Azad University and with cooperation from Shahroud University of Medical Sciences. Dr. Razavianzadeh was the supervisor, and Dr. Mousavi was the consulting professor for the thesis.

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