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Comparison of midazolam versus captopril in patients with uncomplicated hypertensive urgency in emergency ward: Double-blind randomized clinical trial

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Original Article

Abstract

BACKGROUND: The urgency of uncomplicated blood pressure (BP) is known as a sudden rise in BP. The aim of this study was to evaluate the intravascular administration of midazolam as an emergency care to control BP against captopril in patients with uncomplicated hypertension (HTN).

METHODS: The present study was a double-blind parallel randomized clinical trial (RCT) study that was performed on patients with urgent HTN referred to Imam Hossein Hospital in Shahroud, Iran, in 2018. Patients with BP higher than 180/110 mmHg and with healthy vital organs were selected randomly and allocated into three groups of 43 participants. All patients' BP in both arms, and after a period of 10 minutes in the left arm, was checked and after administering the medication was checked again for 4 times of 15 minutes till 1 hour complete.

RESULTS: There were significant differences between systolic (P = 0.024), diastolic (P = 0.001), and mean BP (P = 0.009) in the midazolam group before and after treatment. The group of midazolam and captopril showed the greatest reduction of BP before, in the middle, and after carrying out the treatment methods. As such, systolic, diastolic, and mean BP showed 23.5% (P = 0.047), 17.4% (P = 0.021), and 20.5% (P = 0.031) reduction, respectively.

CONCLUSION: Midazolam can be used as an effective and low-risk drug for lowering BP. Midazolam also has a faster effect on lowering BP.

Keywords: Hypertension; Midazolam; Captopril; Emergency Medicine; Clinical Trial

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Introduction

High blood pressure (BP) can cause major problems in patients with high BP with a condition called critical BP, which usually occurs in less than one percent of cases.[1] In patients with hypertensive crisis, this problem suddenly increases BP as possible to vital organs such as heart, kidney, brain, and eye damage. In such cases, patients' BP should decrease within a few minutes. Therefore, appropriate treatment serves crucially as a controller of BP.[2] Any lack of immediate and appropriate dealing over hypertension (HTN) crisis results in early death due to kidney failure.[3]

In the treatment of patients with critical HTN, various drugs are used orally or sublingually. Until 1996, nifedipine was used sublingually as directed to reduce BP in emergency patients.[4-6] Later, studies revealed and recommended to use the captopril over nifedipine due to the harmful and deadly effects of nifedipine including sudden fall in BP, brain and heart ischemia, and sudden death.[6-9] In several studies, the effect of 25 mg sublingual captopril on lowering BP has been compared with 10 mg of sublingual nifedipine, which had approximately the same effect on lowering BP; however, no significant side effects were observed with sublingual captopril. Nifedipine lowers BP faster than captopril, which causes side effects.[10-12]

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Midazolam, a new benzodiazepine, can decrease the BP by taking the anxiety as well as stress into control. It can help lower BP by reducing stress and anxiety; however, a few studies have investigated the clinical effectiveness of midazolam on BP.[13-16] Some side effects such as airway obstruction are expected if the medication is exceeded the stated doze.[17,18] It is the most common preventative drug in outpatient treatment due to its rapid onset, short half-life, safety, and mild side effects, as well as its cost-effectiveness.[19] However, a comparative study of intervention methods is required to provide evidence in case of the effectiveness of midazolam. This paper, thus, compares the efficacy of controlling BP in both midazolam and captopril administration in patients diagnosed with uncomplicated urgent HTN.

Materials and Methods

Study design and setting: The present study was a double-blind randomized clinical trial (RCT) performed on patients with hypertensive crisis presenting to emergency department of Imam Hossein Hospital, Shahroud, Iran, from December 2018 to May 2019, to evaluate the efficacy of midazolam in hypertensive crisis management. The study protocol was approved by Ethics Committee of Shahroud University of Medical Sciences under the number IR.SHMU.REC.1397.076 and registered on Iranian Registry of Clinical Trials (IRCT) under the number IRCTID IRCT20181010041299N1. Researchers adhered to the principles of Declaration of Helsinki and confidentiality of patients' information throughout the study period.

Participants: All adult patients with hypertensive crisis were enrolled in this study. The allocation of patients to treatment groups was done using simple randomization and Random Allocation Software. Patients with a systolic and/or diastolic BP higher than 180/110 mmHg, aged between 18-80 years were included in this study and asked to sign the informed consent by stating their agreement. Patients with the left-sided chronic heart failure, chronic renal failure, cardiovascular diseases, history of brain and heart stroke, usage of benzodiazepines during the last week, usage of muscle relaxation medications such as baclofen or antianxiety medications such as zolpidem or buspirone, allergy to captopril/midazolam, pregnancy and infant, an acute HTN condition in which doctor prefers rather midazolam and captopril, and patients with a difference of 15 mmHg for BP indicated by each arm were excluded (Figure 1).

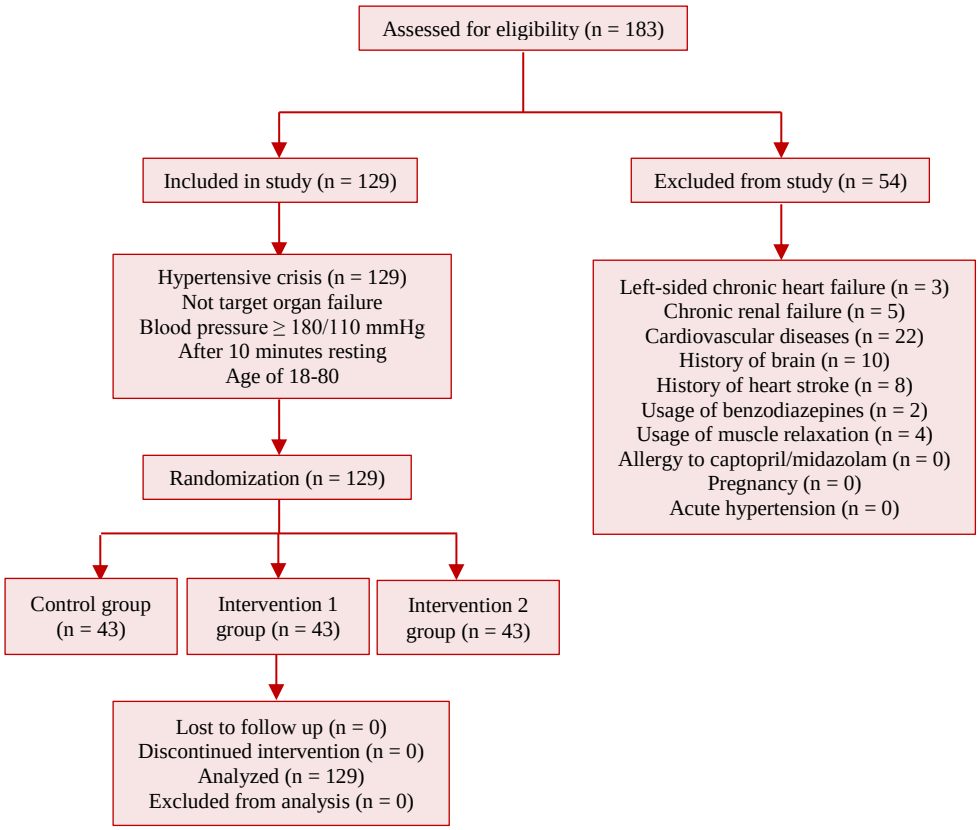

Figure 1. Flow diagram of patient selection

Intervention: After selecting the patients meeting the inclusion criteria, the participants were randomly allocated to one of the study groups. Comparison was performed for the two main drugs, captopril (25 mg orally) (Exir Pharmaceutical Co., Tehran, Iran) and midazolam (1 mg intravenous) (Exir Pharmaceutical Co., Tehran, Iran). This research, on the other hand, employed two placebos including vitamin B and distilled water instead of captopril and midazolam, respectively, for patients to receive.

Simple randomization was used for randomization. Using randomization software (version 1.0.0), individuals were divided into two treatment groups and one control group. In control group, captopril tablets and injected placebo distilled water, in intervention group 1, midazolam injection and placebo vitamin B tablets, and in intervention group 2, midazolam injection and captopril were prescribed.

Based on mean and standard deviation (SD) of systolic BP in patients with HTN in Yilmaz et al. study,[20] and considering the significance level of 0.05 and statistical power of 80%, the total sample size reached the number of 129 by considering 10% loss of our samples. Thus, each group of treatment added 43 more participants to investigate. Initially, the numbers 1 to 129 were written on 129 envelopes, respectively. Then, in each envelope, a sheet containing the code of the type of treatment of each patient, which was specified based on the Random Allocation Software and determined the treatment of each patient, was placed. After entering or identifying each patient according to the entry criteria, an envelope was selected in which the type of treatment was coded. The patient and the statistician were blind to the type of drug used. For blinding patients and analyzing the type of drug used in each individual, a placebo was used, and each medical group was assigned a code that only an emergency specialist could interpret.

A trained nurse was responsible for monitoring and evaluating patients' BP and recording their information. In addition, one of the emergency medicine residents under the supervision of an emergency medicine specialist was responsible for random allocation and execution of interventions.

Data gathering: Data of the patients were collected based on a checklist that represented two sections. The first section asked for demographic information such as age, location, and sex. The second one represented patients with the required information on the procedure of treatment including systolic/diastolic BP, pulse and breath rate, side effects, etc.

All patients' BP in both arms, and after a period of 10 minutes in the left arm, was checked by the nurse doing the shift work. BP in patients was also checked while laying them on the bed and on the standard basis, using a mercury manometer. If a patient was reported to have a systolic and diastolic BP higher than 180/110 mmHg after the period of 10 minutes or more, the patient must be transferred to one of the groups of treatment after revising exclusion and inclusion criteria by the medicine specialist. The patients in each group of treatment were given medications in accordance with the treatment protocols stated. On the standard basis, all patients' BP was checked for 4 times of 15 minutes after administrating treatment methods to compare them in details. If patients experienced any side effects after giving them any specific medication and in the middle of checking the BP, the patient should visit the medicine specialist for the required treatment and stop attending the study.

In the case of lack of success to lower patients' BP after checking the BP for the last time, it was instructed to employ other treatment methods to control the BP in the patient and avoid giving the medications investigated in this study.

Outcome: This study mainly focused on the outcome of BP in patients. The secondary outcome that was investigated was about the side effects of the treatment methods. To calculate the mean arterial pressure, the systolic and diastolic BP were calculated by the sum of systolic pressures and two times of diastolic pressure divided by the number of three. The nurse specialist checked the patients for the interval of 15 minutes to give the required medications to patients in the case of developing some side effects in them, including drowsiness and shortness of breath.

Statistical analysis: The statistical analysis was conducted in SPSS statistical software (version 16, SPSS Inc., Chicago, IL, USA) with intention to treat analysis method. The normality distribution of the quantitative data was determined using Kolmogorov-Smirnov test. Continuous and categorical variables were presented as mean ± SD and frequency and percentage, respectively.

One-way analysis of variance (ANOVA) was used to compare quantitative variables in the three treatment groups. Chi-square analysis was used to measure qualitative variables and repeated measures analysis was used for comparison of quantitative and qualitative variables. $P \leq 0.05$ was considered as statistical significance level.

The number needed to treat (NNT) is a useful way of reporting the results of randomized controlled trials. In a trial comparing a new treatment with a standard one, the NNT is the estimated number of patients who need to be treated with the new treatment rather than the standard treatment for one additional patient to benefit.[21] NNT (Benefit) and number needed to harm (NNH) are the number of patients needed to be treated for one additional patient to benefit or to be harmed, respectively. The 95% confidence interval (CI) was calculated according to Daly[22] and was reported as suggested by Altman.[21] MedCalc (version 20.008) software was used to calculate NNT (MedCalc Software Ltd. Relative risk calculator (Version 20.008; accessed June 13, 2021).

Results

Baseline characteristic of the patients: Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow chart of patient selection. The study was investigated on 129 patients including 45 men (34.9%) and 84 women (65.1%). 106 patients (82.2%) lived in the city and 23 patients (17.8%) lived in the village. The average age of the participants was 61.76 ± 11.44 years. As table 1 shows, no significant difference was observed between groups in terms of gender (P = 0.398), location (P = 0.809), age (P = 0.634), history of diseases (P = 0.858), and history of BP (P = 0.956).

Response to treatment: Measuring BP at different times (Table 2) in the all three groups before and after treatment showed a significant difference among systolic, diastolic, and mean BP compared before and after the treatment. Mean of systolic BP in repeated time measurements in each treatment group was different and decreased. On the other hand, a significant level of systolic BP between treatment groups (P = 0.284) showed no significant difference between treatment groups in terms of changes in systolic BP. Mean of diastolic BP in repeated time measurements in each treatment group was different and decreased. On the other hand, a significant level of diastolic BP between treatment groups (P = 0.127) showed no significant difference between treatment groups in terms of changes in diastolic BP.

As it can be seen in table 2 and figure 2, the average of systolic BPs was decreased to 20.6 ± 12.0, 19.9 ± 7.5, and 23.5 ± 10.9 for the groups of midazolam, captopril, and midazolam and captopril, respectively. The analysis results indicated that there was no significant difference among all three groups in terms of lowering the BP (P = 0.239), although the greatest reduction of intragroup has targeted the group of both midazolam and captopril administration.

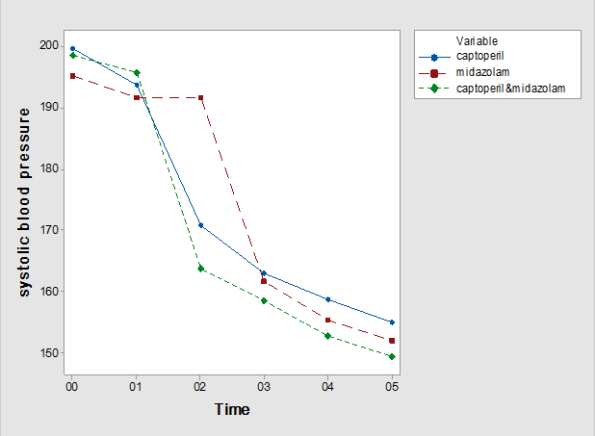

Figure 2. The decreasing pattern of systolic blood pressure in treatment groups

Table 1. Patients' baseline characteristics in the treatment groups

Variables	Level	Groups			P
		Midazolam	Captopril	Midazolam/captopril	
Gender	Men	18 (41.9)	15 (34.9)	12 (27.9)	0.398*
	Women	25 (58.1)	28 (65.1)	31 (72.1)	
Location	City	36 (83.7)	34 (79.1)	36 (83.7)	0.809*
	Village	7 (16.3)	9 (20.9)	7 (16.3)	
Age (year)		61.95 ± 10.43	62.84 ± 9.51	60.49 ± 14.03	0.634**
History of disease[a]	Yes	36 (83.7)	38 (81.4)	34 (79.1)	0.858*
	No	7 (16.3)	8 (18.6)	9 (20.9)	
History of hypertension	Yes	33 (76.7)	33 (76.7)	34 (79.1)	0.956*
	No	10 (23.3)	10 (23.3)	9 (20.9)	

Data are reported as mean ± standard deviation (SD) and frequency and percentage for continuous and categorical variables, respectively.
[a]Diabetes, blood lipids, chronic kidney disease, cardiovascular disease; *Chi-square test; **One-way analysis of variance (ANOVA) test

Table 2. Mean blood pressure at different times in treatment groups

Variables	Groups	Time of blood pressure measurements (minute)						10-60*	P¥
		0	10	15	30	45	60		
Systolic	Control	199.6 ± 17.4	193.6 ± 15.5	170.8 ± 20.2	163.0 ± 17.7	158.7 ± 18.0	155.0 ± 20.6	19.9 ± 7.5	0.001
	Intervention 1	195.1 ± 15.5	191.7 ± 13.7	166.8 ± 19.5	161.7 ± 21.0	155.3 ± 22.4	151.9 ± 24.5	20.6 ± 12.0	0.024
	Intervention 2	198.6 ± 12.9	195.7 ± 13.0	163.7 ± 23.2	158.4 ± 23.4	152.7 ± 22.6	149.4 ± 23.0	23.5 ± 10.9	0.047
	P**	0.364	0.435	0.289	0.585	0.430	0.526	0.239	0.284€
Diastolic	Control	107.0 ± 12.6	103.9 ± 10.2	97.0 ± 11.6	93.8 ± 10.1	91.4 ± 10.6	89.4 ± 8.9	13.5 ± 8.9	0.008
	Intervention 1	107.3 ± 11.5	104.7 ± 9.6	94.3 ± 10.3	89.5 ± 10.8	86.9 ± 9.8	86.2 ± 10.9	17.4 ± 9.5	0.001
	Intervention 2	106.4 ± 11.3	104.7 ± 9.1	93.0 ± 11.7	90.1 ± 11.1	87.4 ± 9.6	86.0 ± 9.1	17.4 ± 9.3	0.021
	P**	0.931	0.904	0.232	0.133	0.086	0.203	0.083	0.127€
Mean	Control	137.9 ± 11.7	133.8 ± 10.0	121.6 ± 12.9	116.8 ± 11.2	113.8 ± 12.0	111.2 ± 11.9	16.7 ± 7.0	0.001
	Intervention 1	136.5 ± 10.2	133.7 ± 7.4	118.4 ± 11.5	113.6 ± 12.4	109.7 ± 12.5	108.1 ± 14.2	19.1 ± 9.8	0.009
	Intervention 2	137.1 ± 9.3	135.0 ± 8.3	116.5 ± 14.5	112.9 ± 13.4	109.2 ± 11.8	107.1 ± 11.4	20.5 ± 8.2	0.031
	P**	0.833	0.732	0.195	0.286	0.162	0.296	0.123	0.174€

Control group: Captopril; Intervention group 1: Midazolam; Intervention group 2: Midazolam and captopril
Data are reported as mean ± standard deviation (SD)
*Percentage reduction of blood pressure between times 10-60 minutes; **P-value of between-group comparisons obtained from one-way analysis of variance (ANOVA) test; ¥P-value of within-group comparisons obtained from repeated measures ANOVA; €P-value of between-group comparisons obtained from repeated measures ANOVA test.

Besides, the diastolic BP dropped in the groups of midazolam, captopril, and midazolam and captopril indicating the percentages of 17.4 ± 9.5, 13.5 ± 8.9, and 17.4 ± 9.3, respectively. Despite the highest reduction in the group of captopril, there was no significant difference among the groups of treatment (P = 0.083) in terms of diastolic BP decrease. With respect to the average of BP in all three groups, it was observed that the midazolam, captopril, and midazolam and captopril groups showed the average BP reduction of 19.1 ± 9.8, 16.7 ± 7.0, and 20.5 ± 8.2. Note that this reduction obtains no significant difference in all three groups (P = 0.123). Comparison of treatment groups did not show a significant difference in terms of lowering BP (Figure 3 and Table 3).

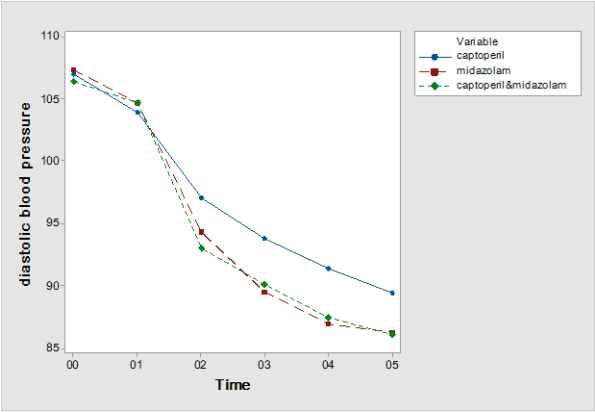

Figure 3. The decreasing pattern of diastolic blood pressure in treatment groups

In terms of side effects in each of the treatment groups, people were examined at different times of the study. A total of 7 patients (5.4%) of the total subjects underwent complications from the drug. Of these, 3 were in the midazolam and placebo group, 1 was in the captopril and placebo group, and 3 were in the midazolam and captopril group. The results showed that there was no significant difference between the three treatment groups in terms of the side effects of drug use (P = 0.547).

Comparison of systolic BP between the two groups of captopril (control group) and midazolam (intervention group) showed NNT (Harm) = 10.75 [3.495 (Harm) to ∞ to 9.989 (Benefit)]. Comparison of captopril with midazolam and captopril (intervention 2) also showed NNT (Benefit) = 14.33 [(7.393 (Harm) to ∞ to 3.639 (Benefit)]. Comparison of diastolic BP in the two groups of captopril (control group) and midazolam (intervention group) showed that NNT (Harm) = 10.75 [3.495 (Harm) to ∞ to 9.989 (Benefit)]. Comparison of captopril with midazolam and captopril (intervention 2) also showed that NNT (Benefit) = 21.50 [7.588 (Harm) to ∞ to 4.448 (Benefit)].

Discussion

In this study, the highest BP reduction in the first measurement (15 minutes after prescription) was observed after the medication administration in all three treatment groups and gradually met the maximum reduction. As such, the BP decreased deliberately and no brain or cardiac side effects were observed in the patients. There was no significant difference in systolic, diastolic, and mean BP in all three treatment groups. According to the guidelines designed in the present study, the target group was patients who did not have end organ damage; therefore, their BP was checked at 15-minute intervals, so that if there was an increase or no acceptable response, they would be routinely treated and excluded from the study. In this way, we could completely control the group that received midazolam only and prevent them in the event of rapid side effects.

But in all three measurements, midazolam and captopril groups showed the greatest reduction in BP, which can be due to the simultaneous effect of the two medications on BP. There was no significant difference between midazolam group and captopril group in terms of systolic BP reduction, while diastolic BP and the mean BP in the midazolam group decreased greater than the captopril group.

Table 3. Comparison of blood pressure in treatment groups using Tukey test

Variables	Groups		Mean difference	P
Systolic	Control	Intervention 1	2.70	0.751
		Intervention 2	4.21	0.500
	Intervention 1	Intervention 2	1.51	0.914
Diastolic	Control	Intervention 1	2.77	0.301
		Intervention 2	2.86	0.277
	Intervention 1	Intervention 2	0.90	0.999
Mean	Control	Intervention 1	2.74	0.424
		Intervention 2	3.31	0.288
	Intervention 1	Intervention 2	0.56	0.964

Although this difference was not statistically significant, it could indicate that midazolam peak effect is greater in reducing BP.

All three groups of this investigation showed the highest BP reduction within 15 minutes after performing the treatment, while in many studies, the most reduction of pressure in patients with hypertensive crisis occurred 30 minutes after medications. This can be due to different levels of measuring in different studies that were not equal. Some investigations on captopril showed the peak effect timings of a 25-mg sublingual dose. It was shown to be 30 minutes after administration and continued for at least two hours.[20,23-25]

In the study by del Castillo et al., 12.35 mg captopril resulted to a decrease of 66% in the diastolic BP in patients with critical HTN within 30 minutes, as the diastolic pressure reached below 100 mmHg.[26] In a survey conducted in Turkey, 90% of people with diastolic BP higher than 120 mmHg reported to have a reduction of BP using 25 mg sublingual captopril with the action time of 60 minutes.[27] In Kazerani and Haji Moradi study, more than 65% of the patients with diastolic BP observed a decrease within 30 minutes after administrating captopril.[28]

The present study showed greater BP reduction in the midazolam group compared to the captopril group. Although observing the effect of this drug on decreasing diastolic BP and the average BP showed no significant difference between treatment groups, these results can be indicative of the efficacy of midazolam in reducing the BP in the patients of hypertensive crisis. This can also be due to the effects of midazolam on physiological and biological stresses that can lead to a greater reduction in BP. In a study by Jones et al., that was performed on animals, midazolam reported to be able to decrease the BP about 10% to 20% on arterial BP after performing the injection.[29]

A study by Forster et al. on several volunteers showed a medium decrease in arterial BP by midazolam.[30] In a study by Heikkila et al., a rapid decline in systolic BP between 24% and 32% and diastolic BP between 29% and 33% was observed.[31]

Conclusion

Midazolam can be used as an effective and low-risk drug for lowering BP. Midazolam also has a faster effect on lowering BP. Considering the fact that it is a sedative drug, it is also beneficial in the rapid reduction of BP associated with stress and has several therapeutic effects.

Limitations: One limitation of our study was that the sample size might be insufficient to detect the exact drug effects. Further clinical trials with larger sample sizes and longer follow-up should therefore be performed to identify its role. Another limitation of this study is the lack of measurement of stress and anxiety in patients with hypertensive crisis. Regarding the effect of stress and anxiety on HTN, and considering midazolam as an effective drug in reducing stress, it is recommended to measure stress and anxiety in these patients using standard instruments.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

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