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Original Article

Evaluation of Factors Affecting the Efficacy of Nitroglycerin Infusion in Patients with Hypertensive Crisis

Kamal Khademvatan[a], Farzaneh Gerami[a,b], Samin Abbaszadeh[b], Hamid Soraya[b*]

[a]Department of Cardiology, Seyyed-al-Shohada Heart Center, Urmia University of Medical Sciences, Urmia, Iran, [b]Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran.

Abstract

Hypertensive crisis is a severe elevation in blood pressure (BP) that requires urgent reduction in BP to prevent or reduce target organ damage. The antihypertensive effects of nitroglycerin have been proven, but there are limited reports on the effects of various factors on the effectiveness of nitroglycerin in the treatment of hypertensive crisis. The purpose of this study was to evaluate the effects of diabetes, history of hypertension and age as well as gender differences in the effectiveness of nitroglycerin in patients with hypertensive crisis. This study included 76 patients with hypertensive crisis. For management, nitroglycerin initially started at 5 µg/min by intravenous infusion and, if needed, every 3 to 5 min, 5 µg/min was added to the above dose to a maximum of 20 µg/min as long as the blood pressure level reaches to the desired level. The results showed that the mean time of reduction of BP to the desired level in patients with history of hypertension and diabetes alone or both diseases, increased significantly in comparison to patients without these underlying diseases ($P<0.01$, $P<0.01$ and $P<0.05$ respectively). The results also demonstrated that there is a significant difference between patients younger than 45 and over 65 years with patients aged 45-65 ($P<0.05$). There is no difference between two genders in each group ($P>0.05$). In conclusion, patients with diabetes and/or history of hypertension are more resistant to pressure lowering effect of nitroglycerin in hypertensive crisis. Patients under 45 years of age as well as the elderly are also resistant. Therefore, it is advisable for physicians to choose the appropriate treatment for the desired outcome, considering the patient's condition.

Keywords: Blood pressure, Diabetes, History of hypertension, Hypertensive crisis, Nitroglycerin.

Corresponding Authors: Hamid Soraya, Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran
Tel: 984432754996
Email: Soraya.h@umsu.ac.ir
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1. Introduction

Hypertension is an extremely common disorder that affects about one billion individual worldwide and is one of the most important risk factors for several types of heart diseases such as coronary heart disease, heart failure, atrial fibrillation and sudden cardiac

death [1-3]. Hypertension is responsible for about 7.1 million deaths every year [4]. Hypertensive crisis represent a small fraction of the wide range of high blood pressure [5]. Hypertensive crisis is severe elevation in blood pressure that is diagnosed when systolic blood pressure is >180 mmHg and diastolic blood pressure is > 120 mmHg and is usually found in patients with essential arterial hypertension [6-8]. Hypertensive crisis occurs as hypertensive urgency and hypertensive emergency, which depends on whether there is damage in the target tissue, or not. Hypertensive urgency refers to a condition with a severe rise in blood pressure without progressive dysfunction of target organs (heart, brain, kidneys and arteries), while hypertensive emergencies are associated with a severe increase in blood pressure and also acute damages to target organs, so it is considered as a life-threatening state [8, 9]. Patients with hypertensive crisis should be admitted to the intensive care unit in order to monitor their blood pressure and receive the appropriate parenteral agent [10]. A wide variety of agents are used for the treatment of hypertensive crisis with different mechanisms of action. One of these agents is nitroglycerin [11]. Nitroglycerin is a vasodilator that is used as an antianginal and antihypertensive drug, which reduces blood pressure by direct vasodilatory effect on peripheral capacitance and resistance vessels and by reducing preload and cardiac output [11, 12]. However, many factors may affect the patient's response to antihypertensive medications [13]. For example, one study showed that in women plasma levels of metoprolol and propranolol are higher than the levels in men due to the slower clearance and low volume of distribution, which may lead to a greater decrease in systolic blood pressure and heart rate than men [14]. Another study showed that the antihypertensive response of captopril with hydrochlorothiazide is greater in patients aged over 55 in comparison to younger patients [15]. Therefore, factors such as gender, age, race, comorbidities and medical condition have an effect on achieving the therapeutic goal in controlling the blood pressure [16]. Since hypertensive crisis is one of the emergencies that requires prompt medical intervention, it is important to consider the effects of mentioned factors in the effectiveness of the drugs used. The primary target of therapy in hypertensive crisis is to alleviate mean arterial blood pressure by no more than 25 percent (within the first hour), then if stable, to 160/100–110 mmHg within the next 2–6 hours [6, 10]. Therefore, it is advisable for the physician to consider effective therapies to control the patient's blood pressure [13]. Since there are not enough studies on the effects of gender, age, history of diabetes and high blood pressure on the effectiveness of nitroglycerin in hypertensive crisis, the purpose of this study was to evaluate the effects of these factors on the effectiveness of nitroglycerin in patients with hypertensive crisis.

2. Materials and Methods

This study included 76 patients, who were hospitalized in Emergency Medical Services of the Urmia Seyyed Al-Shohada Hospital with hypertensive crisis. Hypertensive crisis is determined by an intense increase in blood pressure (levels of systolic blood pressure >180 mmHg and/or diastolic blood pressure >120 mmHg) according to Guidelines of the U.S. National Institutes of Health (National Institutes of Health, National Heart, Lung, and Blood Institute) [6]. According to the treatment protocol of the Seyyed Al-Shohada Hospital, the respective physician admitted patients after diagnosis of hypertensive crisis and then nitroglycerin is administered at a rate of 5 μg/min in normal saline via intravenous infusion. If needed, the dose is increased 5 μg/min every 3 to 5 min to a maximum of 20 μg/min until the blood pressure level reaches the desired level [6]. The desired level of blood pressure in hypertensive crisis is to reduce mean arterial pressure by no more than 25% within the first hour, then if stable, to 160/100-110 mm Hg within the next 2 to 6 hours according to clinical practice guidelines [6, 10]. After stabilization of the patient's blood pressure, the time required to reach to the desired blood pressure level was recorded. Patients were divided into four groups according to their history of hypertension or diabetes in order to evaluate the effect of history of high blood pressure or diabetes on the response to nitroglycerin in hypertensive crisis. The first group had no history of hypertension and no diabetes, the second group only had a history of hypertension, the third group only had a history of diabetes, and the fourth group had both a history of hypertension and diabetes. The effect of gender on nitroglycerin efficacy was also evaluated in each group. In addition, the effect of age on the time it took to reach to desired blood pressure level were evaluated in response to nitroglycerin in the studied patients.

2.1. Statistical Analysis

Data were analyzed using SPSS.24 software. Chi-square test was used to identify groups by age and gender. Kruskal-Wallis (KW) nonparametric test was used to compare the mean values between groups and Mann-Whitney nonparametric comparison was used for post hoc KW test. Mann-Whitney nonparametric test was used to compare the mean values between two genders in each group. One-way ANOVA and a LSD post test was performed to compare the mean values of ages between the groups. Mean±SD were used to express data. The differences between the groups were considered statistically significant if $P<0.05$.

2.2. Ethics

After demonstrating the aim of the study, verbal consent was obtained from the patients and ethical principles were observed in all stages of this research. (Ethical code: ir.umsu.rec.1396.171)

3. Results and Discussion

Hypertension is one of the most common cardiovascular diseases [17]. Hypertensive crisis is an acute increase of blood pressure (180/120 mmHg) accompanied with end organ damage [10, 18]. Nitroglycerin is a potent venodilator with a marked arterial dilation effects at high doses as well. Nitroglycerin infusion is recommended as one of the treatment choices in blood pressure control in acute hypertensive crisis [6, 18]. Since there is a little information about the effect of various factors and comorbidities on the efficacy of cardiovascular medications, therefore, drug interventions are usually ineffective. The present study investigated some comorbidities and factors influencing the effectiveness of nitroglycerin on blood pressure including the history of diabetes, history of previous high blood pressure, gender and age, in patients with hypertensive crisis. The results of this study, for the first time, indicated that diabetic patients, patients with history of hypertension and patients under 45 years old, as well as the elderly patients, are resistant to the blood pressure-lowering effects of nitroglycerin.

In the present study, with the aim of investigating the effective factors on the efficiency of nitroglycerin in controlling blood pressure in patients with arterial hypertension admitted to the Emergency Medical Services of the Urmia Seyyed Al-Shohada Hospital, there was a total of 76 patients: 35 men (46%) and 41 women (54%). Of these, 39 cases (51.3%) had the history of high blood pressure and 21 cases (27.6%) had diabetes mellitus (DM).

According to definitions applied for desired BP level, the blood pressure of all the subjects reached to desired level after 6 hours. The average time for the efficacy of nitroglycerin, (reduction of pressure to the desired level) was 3.24 ± 2.6 (at least 1 hour and maximum 6 hours). According to the results of chi-square analysis, the frequency distribution of data in different groups were similar in gender and age ($P>0.05$) (Table 1).

In the study of the effect of history of hypertension and diabetes, the results showed that the mean time (hours) of the reduction of blood pressure to the desired level in patients with no history of hypertension and no diabetes was 2.28 ± 1.63. However, this value was 3.94 ± 1.96 in patients with history of only hypertension, 4.54 ± 1.63 in patients with history of only diabetes and in the group of patients who have both high blood pressure and diabetes was 4.1 ± 2.46. Therefore, the results demonstrated that the mean time (hours) of the reduction of blood pressure to the desired level in patients with a history of hypertension and diabetes only or with both diseases are significantly higher than that in patients without a history of hypertension and diabetes (Figure 1; $P<0.01$, $P<0.01$ and $P<0.05$ respectively). One of the important results of this study is the resistance of diabetic patients with hypertensive crisis to the blood pressure lowering effects of nitroglycerine. Studies have shown that some diseases such as diabetes have a high prevalence of

hypertension [19]. Previous studies also have indicated that patients who have diabetes besides hypertension are more resistant to antihypertensive drugs than patients with hypertension alone [20]. One of the causes of resistance of diabetic patients to the antihypertensive drugs may be due to the diabetes-induced micro- and macro-vascular complications [21]. Insulin resistance and diabetes can cause arterial stiffness in all age groups and reduce nitric oxide synthesis. As a result, it can increase blood pressure [22]. On the other hand, studies have shown that there is a relationship between adipocytokines, diabetes and hypertension [19]. Adipocytokines are cytokines that are secreted from adipose tissue and have several physiological functions such as insulin sensitization, proinflammatory properties and vascular homeostasis [19, 23]. Numerous studies have shown that adipokines play a major role in the complications of diabetes, including refractory hypertension and cardiovascular disease [24, 25]. Lee et al. showed that adipokines are strongly associated with high blood pressure [26]. Adipokines are effective in nitric oxide production natriuresis and sympathetic activation, especially in kidneys, leading to sodium retention, systemic vasoconstriction, and hypertension [27, 28]. Therefore, according to the recent findings about the effects of adipokines in the refractory hypertension in diabetic patients, it seems to be one of the causes of resistance in reducing blood pressure in diabetic patients compared with non-diabetics in response to nitroglycerine. Previous studies have reported nitrate tolerance in diabetic patients [29], but the present study investigated the acute effect of nitroglycerin in hypertensive crisis. Since these patients require urgent reduction in blood pressure, nitroglycerin may not be an appropriate treatment option in diabetic patients.

Another important finding of this study was that patients with a history of hypertension are also resistant to the effects of nitroglycerin in hypertensive crisis. Studies demonstrated that uninterrupted use of nitroglycerin can cause loss of pharmacological vasodilatory effects on smooth muscle and this tolerance can be due to impaired tissue response to nitrates and progressive desensitization of blood vessels to nitrate and NO effects [30, 31]. In addition, for a long time, arterial stiffness has been known because of long-term hypertension. However, some studies have also suggested that arterial stiffness may be involved in the pathogenesis of hypertension [32]. Studies have also shown that arterial stiffening is a leading factor for possible changes in systolic hemodynamic load. However, in hypertension, arterial stiffness increases due to the increased pressure distension. Furthermore, a sustained increase in blood pressure can increase matrix synthesis, which ultimately increases vascular thickness and structural stiffness [33]. On the other hand, studies have shown that each type of antihypertensive drugs have different effects on arterial stiffness [34]. Therefore, in agreement with the results of the above studies, it seems that history of previous blood

pressure and uses of antihypertensive drugs can be effective on the efficacy of intravenous nitroglycerin in hypertensive emergencies. Accordingly, patients with a history of hypertension are resistant to the antihypertensive effect of nitroglycerin.

In addition, as can be seen in fig. 2, the difference between the mean time (hours) of the reduction of the blood pressure to the desired level was not significant between men and women in all studied groups (P>0.05). The present study demonstrated that gender does not affect the response to nitroglycerin treatment in hypertensive patients. There are differences in the pharmacokinetics including how the drug is absorbed, distributed, metabolized and eliminated, as well as the pharmacodynamics including the effects of drug concentration at the site of action between men and women [35-37]. However, the results of a study by Ong et al. showed that there was no significant difference in blood pressure control between men and women [38]. Also according to clinical practice guidelines, in general, women respond to antihypertensive drugs similarly to men and only some of the adverse effects can be gender dependent. Therefore, the antihypertensive choice drugs are the same in both genders [10]. In addition, studies have also shown that arterial stiffness increases with aging in both men and women [39]. According to the findings of the present study, the efficacy of nitroglycerin seems to be gender-independent.

Moreover, analysis of variance (ANOVA) to determine dependence between age and mean time of reduction of blood pressure to desired level among all patients with hypertensive crisis was performed. As seen in fig. 3, the mean time (hours) of reduction of blood pressure to desired level in patients younger than 45 years old is 4.23 ± 1.96, in patients with 45-65 years old is 2.83 ± 1.95 and over the 65 years old is 3.96 ± 2.08. There was a significant difference between the mean times of reduction of blood pressure to the desired level in patients younger than 45 years old and over 65 years old with patients aged 45-65 (P<0.05). Aging is usually accompanied by progressive physiological and functional changes in the organs of the body and can alter the response to stimulation of the receptors. Therefore, it can affect the efficacy of drugs by changing the pharmacokinetics as well as the pharmacodynamics [40, 41]. In addition, the pathology of systolic hypertension in the elderly is different from younger ones, which may be due to arterial stiffness and increased vascular resistance [42]. Based on the results of the present study, patients under 45 years old as well as over 65, showed resistance to the blood pressure lowering effects of nitroglycerin.

4. Conclusion

The results of this study showed that patients with diabetes and a history of hypertension and also patients under 45 years, as well as the elderly patients are more resistant to pressure lowering effect of nitroglycerin in hypertensive crisis. Therefore, it is advisable for physicians to choose the

appropriate treatment for the desired outcome, considering the patient's condition.

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Tables:

Table 1. Frequency distribution of patients in groups by age and gender.

		No HTN + No DM		**HTN + No DM**		**DM + No HTN**		**HTN + DM**		**P-Value**
		(N)	**(%)**	**(N)**	**(%)**	**(N)**	**(%)**	**(N)**	**(%)**	
Gender	M	13	50	12	41.37	4	36.36	6	60	0.656
	F	13	50	17	58.62	7	63.63	4	40	
Age	<45	1	3.84	9	31.03	2	18.18	1	10	0.174
	45-65	16	61.53	13	44.82	5	45.45	4	40	
	>65	9	34.61	7	24.13	4	36.36	5	50	

Figures:

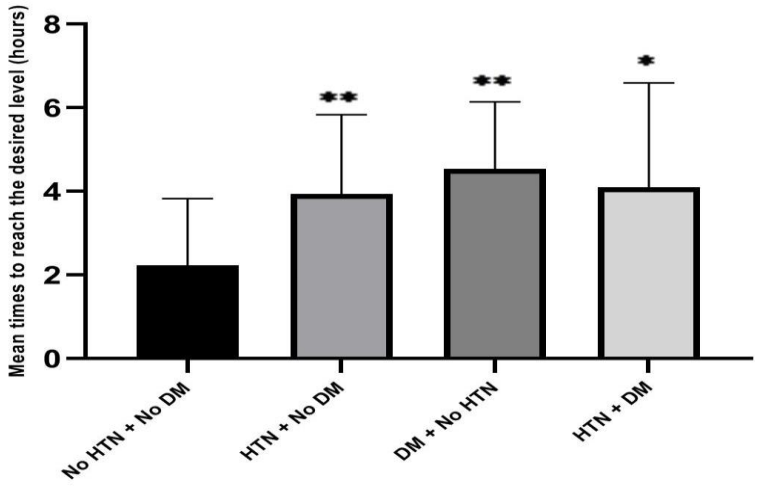

Figure 1. The effects of the history of hypertension and diabetes on blood pressure reduction to desired level in hypertensive crisis in response to nitroglycerine. Data are presented as mean±SD. * *P<0.05*, ***P*<0.01 in comparison to patients with no diabetes and no hypertension using KW and mann-Whitney tests. HTN: Hypertension; DM: Diabetes mellitus.

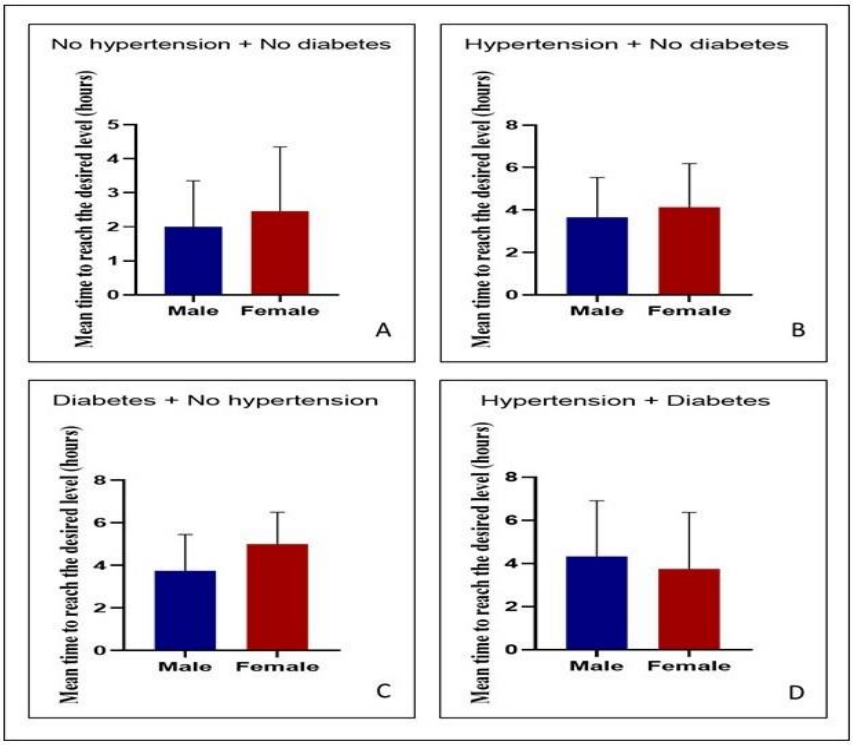

Figure 2. The effect of gender on blood pressure reduction to desired level in hypertensive crisis in response to nitroglycerine in each group. Data are presented as mean±SD. Data analyzed using non parametric mann-Whitney test.

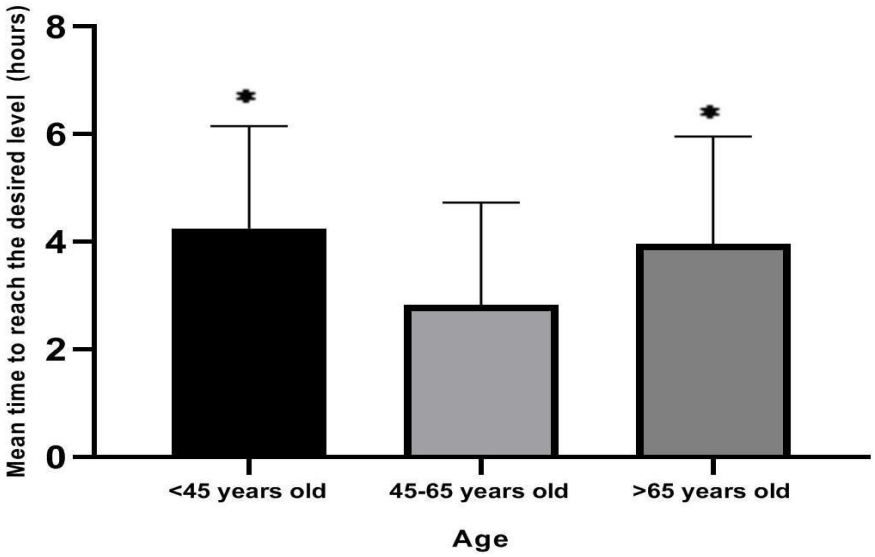

Figure 3. The effects of age on blood pressure reduction to desired level in hypertensive crisis in response to nitroglycerine. Data are presented as mean±SD. **P*<0.05 compared with patients aged 45-65 years using one way ANOVA and LSD *post hoc* test.