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Emergency Room Treatment of Hypertensive Crises

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ABSTRACT

Aim: The aim of the study was to evaluate efficiency of hypertensive urgency treatment using *inhibitors of α1-adrenergic receptors* and *angiotensin converting* enzyme inhibitors–*ACE* inhibitors in the Emergency Room of Outpatient Hospital and Polyclinic „dr Mustafa Šehovic" Tuzla in relation to age, duration and severity of hypertension. Methods: The study was conducted from June 2011 to May 2012 and included 120 patients of both sexes diagnosed with arterial hypertension, aged 40 to 80 with verified hypertensive urgency. The patients were divided into two groups: the control group treated with sublingual captopril and the experimental group treated intravenously with urapidil. Results: The results show that the largest number of patients belonged to age group from 60 to 69 years (34,16%), and the average age was 58 (11). The largest number of patients (38,0%) had verified hypertension for 11 to 20 years. The average systolic/diastolic artery blood pressure at reception was 213 (19) / 130 (4) mmHg. The average systolic/diastolic artery blood pressure after the first dose of 12,5 mg captopril in the control group was 177,42 (10,91) / 112,33 (3,50) mmHg, while after the first dose of 12,5 mg urapidil it was 179,25 (16,62) / 110,33 (8,78) mmHg. The average systolic/diastolic artery blood pressure after the second dose of 12,5 mg of captopril in the control group was 152,00 (6,32) / 95,50 (3,76) mmHg, while after the second dose of 12,5 mg of urapidil it was 152,55 (7,17) / 95,29 (5,04) mmHg. Conclusion: Urapidil is more efficient in hypertensive urgency treatment, since the decrease of middle artery pressure (MAP) in the group treated with urapidil was statistically significant ($p<0,001$). No statistical significance was found between the efficiency of urapidil and the patient's age, while captopril was more efficient in older patients ($p=0,02$). Also, no statistically significant difference was found between the efficiency of captopril and urapidil in relation to duration of hypertension.

Key words: hypertensive crisis, urapidil, captopril

1. INTRODUCTION

Arterial hypertension is the main independent risk factor in cardiovascular diseases and death rate occurrence in developed, but also in developing countries where our country belongs to. The aim of treatment of patients with hypertensive crisis is to stop damage of target organs (1). World Health Organization defines aortic hypertension as the level of systolic blood pressure of 140 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher in persons who do not take antihypertensive therapy (2).

Hypertensive crises represent a small segment in a wide range or artery hypertension (3). Hypertensive crises are defined as levels of systolic blood pressure >180 mmHg and/or levels of diastolic blood pressure >120 mmHg and are mainly found in patients with essential artery hypertension (4, 5). Hypertensive crises occur as hypertensive urgency and hypertensive emergency, depending on whether or not the vital organ is damaged (6). Hypertensive urgency is a situation with a severe increase in blood pressure without progressive dysfunction of target organs (7).

Hypertensive emergencies are life-threatening states because their outcome is complicated by acute damages of target organs (8). Nearly one billion of world population has hypertension and it is responsible for about 7.1 million deaths every year (9). The incidence of artery hypertension in our country is above 30%, which is statistically about 900,000 of patients with hypertension (10). The incidence/prevalence of hypertensive crises in population is insufficiently discussed in medicine. Hypertensive crises are present in less than 1% of adult population in the US (11). Pathophysiology of hypertensive crises is still unclear. From the aspect of pathophysiology, the disorder of systemic blood flow auto-regulation on the level of arterioles is considered to be a cause for both forms of hypertensive crisis (12).

The primary aim of hypertensive crisis management is to safely reduce blood pressure and stop damage of vital organs, and the therapy can be parenteral, peroral and sublingual (13). The target blood pressure for 3-6 hours is 160/110 mmHg for hypertensive urgency, while diastolic pressure should be 100-105 mmHg for hypertensive emergency (14). Middle artery pressure should not be reduced by more than 25% within the first 24 hours. Although urapidil has peroral use in hypertensive urgency management, this therapy can be administered parenterally, as shown in Woisetschläger et al, a study which compares the efficiency of intravenous use of urapidil and peroral use of captopril (15).

The aim of the study was to evaluate efficiency of hypertensive urgency treatment using inhibitors of α1-adrenergic receptors and angiotensin converting enzyme inhibitors–ACE in relation to age, duration and severity of hypertension.

2. EXAMINEES AND METHODS

The paper shows the results of prospective study which evaluates efficiency of blockers of α-1-adrenergic receptors (urapidil) and angiotensin-converting enzyme inhibitors–ACE inhibitors (kaptopril) in hypertensive urgency treatment The study was conducted in the Emergency Room of Outpatient Hospital and Polyclinic „dr Mustafa Šehović" Tuzla from June 2011 to May 2012. It included 120 patients with hypertensive crisis (hypertensive urgency) of both sexes (60 men and 60 women) aged from 40 to 80 who came to the Emergency Room. Considering the duration of hypertension, the patients were divided into those who had suffered from hypertension for less than five years, those who had suffered from hypertension from five to ten years, those who had suffered for eleven to twenty years and those who had suffered from hypertension for more than twenty years.

Hypertensive crisis was defined on the basis of their systolic pressures >180 mmHg and/or diastolic pressure >120 mmHg according National Institutes of Health; National Heart, Lung, and Blood Institute (5).

Inclusion criterion was presence of hypertensive urgency. The study did not include patients with hypertensive emergency, those with mental illnesses, those in terminal stage of malignant disease, patients on dialysis, on cytostatic therapy and long-term corticosteroid therapy, patients who have combination of risk diseases (diabetes mellitus, state after myocardial infarction and cerebrovascular insult), women using contraception, patients who had cocaine or amphetamine overdose, and those who used urapidil in their antihypertensive therapy and those who had been using captopril before they came to the Emergency Room. The study also excluded the patients who had been using their antihypertensive therapy four to six hours before they came to ER. The patients who were included in the study gave their written consent stating that they voluntarily participated in the study, according to the Code of Ethics (16).

We measured blood pressure of each patient using mercury sphygmomanometer with the cuffs sized 34,3x11x25,3 cm while patients were sitting after a 5 minutes rest.

The patients with hypertensive urgency were then divided into two groups: experimental and control group. The patients from experimental group (30 men and 30 women) were treated with urapidil (i.v.) using slow bolus with the initial dose of 12.5 mg, which was gradually increased up to 25 mg if required, on the basis of blood pressure measurements every thirty minutes in the period of one or two hours. The patients from the control group (30 men and 30 women) were treated with captopril (s.l.), with the initial dose of 12.5 mg, which was gradually increased up to 25 mg, measuring at the same time artery tension every 30 minutes in the period of two hours. The patients from the control and experimental group were treated in pairs, so that one patient from each group (one from control group and one from experimental group was given therapy at the same time and artery tension was measured at the same time to both patients. The values of artery tension were then measured after the prescribed therapy dosage had been administered and after the prescribed time period had passed for both groups, and the effectiveness of the drug was estimated.

In statistic tests we used SPSS 19.0 software. All variables were tested using Kolmogorov-Smirnov test. All variables were described using appropriate measures of central tendencies and dispersion (standard deviation and interquartile range). Quantitative variables were compared using Student's t-test with a correction for unequal variance where needed, i.e. t-test for linked samples for comparison of multiple measurements of the same sample. Comparison of arithmetic means for more than 2 variables was done using one-way ANOVA analysis with post-hoc testing according to Tukey methodology. Significant connections between variables were tested using parameter Pearson correlation. In order to compare efficiency of 2 types of treatments, and considering simple dichotomous key, we used risk analysis with calculation of relative risk reduction for unfavorable outcome, or NNT (Number Needed to Treat) parameter. All confidence intervals were calculated supposing Poison distribution was normal. All tests were performed with the accuracy level of 95% ($p<0,05$).

3. RESULTS

In a prospective study which evaluated efficiency of inhibitors of α-1-adrenergic receptors and angiotensin converting enzyme inhibitors–ACE inhibitors in Emergency Room of Outpatient Hospital and Polyclinic „dr Mustafa Šehović" Tuzla, 120 patients were divided into two groups as described in the methodology section. All the patients in the sample were equal in sex, so that there were 30 men and 30 women in each group, and there was no significant difference in this respect. Most patients (34.16%) were aged 60-69, while 27.50% belonged to the age group 40-49. 27 patients (22.50%) belonged to the age group 50-59, and 19 (14.83%) of them belonged to the age group 70-80. The average age (SD) in the sample was 58 (11) years and ranged from 40 to 80 years of age. In terms of age, there was no statistically significant difference between the two groups (t=0.59; df=118; p=0.56).

The analysis of duration of hypertension in patients with hypertensive crisis showed that 45 patients (38%) had verified hypertension in the duration from 11to 20 years, and 40 of them (30%) had hypertension for 5 to 10 years. 22% of the patients had been treated for hypertension for less than five years, and only 8 patients had hypertension which had lasted for more than twenty years.

Table 1. shows descriptive parameters of mean values of systolic, diastolic and middle artery pressure when the patients came to SHMP. The minimum value of systolic/diastolic pressure was 185/125 mmHg, and the maximum value was 250/140 mmHg. Middle value of artery pressure (TA) according to type of arithmetic mean (AS) (SD) was 157 mmHg (8).

	AS	SD	Minimum	Maximum
Systolic TA at reception	213	19	185	250
Diastolic TA at reception	130	4	125	140
Middle TA at reception	157	8	145	177

Table 1. Descriptive parameters of mean values of systolic, diastolic and middle artery pressure

At reception, every patient received 12.5 mg captopril or 12.5 mg urapidil depending on which group they belonged to. The Table 2 shows that middle value of artery pressure after the first dose of captopril was 134.03 mmHg, with the minimum of 123.33 mmHg and the maximum of 143.33 mmHg, while after the first dose of urapidil the middle value was 133.31 mmHg, with the minimum of 110 mmHg and the maximum of 153,33 mmHg. If we look at all three values, we find a significant drop of TA after the use of therapy (p<0.001).

After the first dose of administered drug and measurement of artery tension further approach to therapy was re-evaluated. 9 patients from the group treated with urapidil (15%) did not have to continue therapy because hypertensive crisis ended already after the first dose. All patients in the group treated with captopril demanded that the treatment be continued with increased dosage, i.e. by adding 12.5 mg until the hypertensive crisis ends. Considering the analysis of risk and efficiency, already after the first dose of urapidil, there was a significant therapeutic advantage for patients treated with it compared to the group treated with 12.5 mg captopril. Relative risk reduction for persistence of high TA was 15% (%95 CI=5.5%-23.6%) with NNT (Number Needed to Treat) of 7 patients.

	Group	AS	SD	Minimum	Maximum
Systolic TA after the first dose	Captopril	177.42	10.91	160	200
	Urapidil	179.25	16.62	150	220
Diastolic TA after the first dose	Captopril	112.33	3.50	100	115
	Urapidil	110.33	8.78	90	125
Middle TA after the first dose	Captopril	134.03	4.84	123.33	143.33
	Urapidil	133.31	10.70	110	153.33

Table 2. Descriptive parameters of values of arthery blood pressure after the first dosage depending on whether the patient belonged to the group treated with captopril or urapidil

	Group	AS	SD	Minimum	Maximum
Systolic TA after the second dose	Captopril	152.00	6.32	140	170
	Urapidil	152.55	7.17	130	170
Diastolic TA after the second dose	Captopril	95.50	3.76	90	100
	Urapidil	95.29	5.04	80	105
Middle TA after the second dose	Captopril	114.33	4.04	106.67	123.33
	Urapidil	114.38	5.35	96.67	126.67

Table 3. Descriptive parameters of artery blood pressure after the second dose depending on whether the patient was in the group treated with captorpril or urapidil

After the administration of the second dose of captopril, or urapidil of additional 12,5 mg, i.e. the total of 25 mg, depending on which group they belonged to, there were no indications for further treatment, which means that the target values of blood pressure were reached. Descriptive parameters related to blood pressure values after the second dose are shown in Table 3. In this case the value of middle artery pressure which was achieved was 114,33 mmHg in patients treated with captopril, and the middle value after the second dose of urapidil was 114,38 mmHg. When we compare these values with the values after the first dose, we can notice a significant fall of artery pressure (p<0,001).

mmHg	Group	N	AS	SD	Difference	p-value
MAP decrease after I dose	Captopril	60	20.08	3.66	7,42 mmHg	<0,001
	Urapidil	60	27.50	5.62		
MAP decrease after II dose	Captopril	60	19.69	3.33	2,63 mmHg	<0,001
	Urapidil	51	22.32	4.18		
MAP decrease after the end of treatment	Captopril	60	39.78	3.95	6,61 mmHg	<0,001
	Urapidil	60	46.39	7.18		

Table 4. Compared values of middle arthery pressure after the first and the second dose in control (captopril) and experimental (urapidil) group. MAP-middle arthery pressure; AS-arithmetic mean; SD – standard deviation

Numeric difference between the values of middle artery pressure (MAP) at different measurements was taken as the main measure of treatment efficiency. After administration of the first dose of 12.5 mg of captopril, or urapidil, we noticed the difference in the decrease of middle artery pressure by 7.42 mmHg. After administration of additional 12.5 mg captopril to all patients from control group and 12.5 mg urapidil to fifty-one patients from experimental group (in 9 of these, the target value of artery pressure was achieved after the first dose of the therapy) we noticed the difference in decrease of middle artery pressure by 2.63 mmHg, so that the decrease of middle artery pressure after the end of the treatment was 6.61 mmHg.

As presented in Table 4, based on the compared values, we can see that in the group treated with urapidil, the decrease of MAP was bigger at the level of high statistic significance ($p<0.001$).

When it comes to the analysis of efficiency of urapidil with regard to the patient's age, we searched for the correlation between the decrease of MAP at the end of the treatment (as a numeric efficiency of the therapy) and age, and we did not find statistically significant correlation ($p>0.05$).

Regarding the efficiency of urapidil in relation to duration of hypertension, we did ANOVA analysis which did not show statistically significant difference in MAP decrease (ANOVA; $F=1.933$; $p=0.135$

The same evaluation was performed for the patients treated with captopril. We found a statistically significant, positive and medium correlation between the patient's age and MAP decrease after the end of the treatment ($r=0.40$; $p=0.02$). This practically means that the older patients had a bigger MAP decrease after administration of captopril. The older the patient the bigger MAP decrease after therapy.

We compared the values of MAP decrease with the duration of hypertension, and did not find statistically significant differences between the groups (ANOVA; $F=3.01$; $p=0.06$).

If we consider the MAP differences in relation to age group, we can see that the biggest difference was found between the groups aged 41 to 50 on the one hand and those aged 51 to 60, on the other. We noticed a correlation between age and MAP decrease in the group treated with urapidil (0.26, with $p=0.044$), while it was 0.334 with $p=0.009$ for the group treated with captopril. Hence, in the group treated with captopril, artery blood pressure reduction was more in correlation with the patient's age.

4. DISCUSSION

In patients with essential hypertension, blood pressure can rise due to secondary causes and occurrence of resistant hypertension and those which manifest as hypertensive crisis (17). Hypertensive crises are life-threatening urgent states characterized by a sudden blood pressure rise. They make more than a quarter of all medical urgencies/emergencies. The fact is that the illness progresses in about 50% of patients with hypertensive crisis to that stage without symptoms, and that, unfortunately, hypertensive urgencies and emergencies are still the least understood and the worst treated acute medical problem (18). 1 billion of people worldwide suffer from systemic hypertension. 1-2% of the patients with hypertension develop acute blood pressure elevation, i.e. hypertensive crisis which requires medical treatment (19). Hypertensive crises can be divided into two categories: hypertensive emergency and hypertensive urgency, depending on presence of acute damage of the target organ; they represent life-threatening states and require urgent treatment and constant monitoring (20).

The average age (SD) of the patient in this study was 58 (11) years and ranged from 40 to 80 years, and the largest number of patients was aged between 60 and 69 (34,16%). In relation to the average age of the patient, similar to our study, Hirschla et al. study of the efficiency of various antihypertensive therapies in the Emergency Department (ED), showed that out of 168 patients included in the study, the average age was 52 +/- 12 years (21) (Hirschl et al, 1996).

At reception, middle artery pressure of the total sample was 157±8 mmHg, with the minimum MAP value of 145 mmHg, and the maximum MAP value of 177 mmHg. In Martin et al., a study which included 452 patients, 273 of whom were hypertensive urgencies, the MAP value was 126±14,4 mmHg, which is lower than the value found in the patients in our study (22).

Although numerous therapies are used in managing hypertensive urgency, most of them per os, we decided to use two therapies in our study: captopril sublingually in the control group and urapidil parenterally in experimental group, similar to the study made by Woisetschläger et al. In the prospective double-blind random study by Woisetschläger et al. which included the total of 69 patients with hypertensive urgency, we compared intravenous administration of urapidil with oral administration of captopril. The patients were randomized so that one group received 25 mg captopril orally and 0,9% NaCl i.v. as a placebo, and the other group received 12,5 mg urapidil i.v. and a placebo per os. The study results show decrease in systolic and diastolic blood pressure of 163(20)/85(12) mmHg for urapidil and 159(17)/88(9) mmHg for captopril (p value 0,38/0,40) (15). In our study, after the end of the treatment, the middle value of systolic/diastolic artery pressure decreased. In the group treated with captopril, it was 152,00 (6,32) / 95,50 (3,76) mmHg, and in the group treated with urapidil 152,55 (7,17) / 95,29 (5,04) mmHg ($p<0,001$). MAP reduction, which represented the main measure of therapy efficiency, after the end of the treatment was 39,78±3,95 mmHg for captopril, and 46,39±7,18 mmHg for urapidil. Hence the difference in MAP reduction was 6,61 mmHg. On the basis of the compared values, we can see that this MAP decrease was more significant in the group treated with urapidil, and it was at the level of high statistic significance ($p<0,001$).

Similar to our study, Woisetschläger et al. showed a significant reduction in blood pressure within the first hour in both groups. The study also showed that both therapies are equally safe and efficient in treatment of

patients with hypertensive urgency (15), which was the aim of the study.

5. CONCLUSION

In the prospective study which included 120 patients, the largest number of patients (34.16%) belonged to the age group between 60 and 69.

The average age (SD) of the patients in the sample was 58 (11) and no significant difference was found between the two groups in relation to age. The largest number of patients (38.0% of the overal sample) had verified hypertension for a period between 11 and 20 years.. The average value of systolic/diastolic artery blood pressure at reception was 213 (19) / 130 (4) mmHg.

The average value of systolic/diastolic artery blood pressure after the first dose of 12.5 mg captopril in the control group was 177.42 (10.91) / 112.33 (3.50) mmHg, while after the first dose of 12.5 mg of urapidil it was 179.25 (16.62) / 110.33 (8.78) mmHg.

The average value of systolic/diastolic artery blood pressure after the second dose of 12.5 mg of captopril in the control group was 152.00 (6.32) / 95.50 (3.76) mmHg, while after the second dose of 12.5 mg of urapidil it was 152.55 (7.17) / 95.29 (5.04) mmHg. After the values of artery blood pressure at reception were compared, and after the therapy was administered, artery pressure dropped significantly ($p<0.001$).

MAP decrease in the group treated with urapidil was more significant, at the level of high statistic significance ($p<0.001$), which leads us to the conclusion that urapidil is more efficient in managing hypertensive urgencies. No statistically significant difference was found between efficiency of urapidil and duration of hypertension. There was no statistically significant difference between efficiency of urapidil and the patient's age.

Captopril was more efficient in older patients who had a bigger MAP drop after administration of this therapy ($p=0.02$). There was no statistically significant difference when we compared efficiency of captopril and duration of hypertension.

CONFLICT OF INTEREST: NONE DECLARED.

REFERENCES

1. Fenves AZ, Ram CV. Drug treatment of hypertensive urgencies and emergencies. Semin Nephrol. 2005; 25(4): 272-280.
2. Anonymus. WHO-International Society of Hypertension Guidelines for the menagment of hypertension. J Hypertension. 1999; 17: 151-183.
3. Aggarwal M, Khan IA. Hypertensive crisis: hypertensive emergencies and urgencies. Cardiol Clin. 2006; 24(1): 135-146.
4. Angelats EG, Baur EB. Hypertension, Hypertensive crisis, and Hypertensive emergency: approaches to emergency department care. Emergencias. 2010; 22: 209-219.
5. Anonymous. National High Blood Pressure Education Program. The seventh report of the Joint National Committe on prevention, detection, evaluation and treatment of high blood pressure. Bethesda (MD): Dept. of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication. 2004; No.04-5230l.
6. Elliott WJ. Clinical features in the management of selected hypertensive emergencies. Prog Cardiovasc Dis. 2006; 48(5): 316-325.
7. Anonymous. Third Joint Task Force of European and other Societies of Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2003; 24: 1601-1610.
8. Feldstein C. Management of hypertensive crises. Am J Ther. 2007; 14(2): 135-139.
9. Varon J. Treatment of Acute Severe Hypertension: Current and Newer Agents. Drugs. 2008; 68(3): 283-297.
10. Laganović M, Kuzmanić D. Kako optimalno liječiti arterijsku hipertenziju. Medicus. 2003; 1(12): 77-83.
11. Anonymous. American Heart Organization. Heart and Stroke Statistical Update. 2001: 4-5.
12. Dimković S, Kirćanski-Obrenović B. Hipertenzivna kriza. Medicinski glasnik. 2007; 12(21): 36-46.
13. Chagas F, Junior M, Antonio F, et all. Prevalence of True Hypertensive Crises and Appropriateness of the Medical Menagement in Patients with High Blood Pressure Seen in a General Emergency Room. Arq Bras Cardiol. 2008; 90(4): 247-251.
14. Slama M, Modeliar SS. Hypertension in the intensive care unit. Hypertension. 2006; 21(4): 279-287.
15. Woisetschläger C, Bur A, Vlcek M, Derhaschnig U, Laggner AN, Hirschl MM. Comparison of intravenous urapidil and oral captopril in patients with hypertensive urgencies. Journal of Human Hypertension. 2006; 20: 707-709.
16. Anonymous. World Medical Association Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects. Helsinki. WHO, 1989.
17. Acelajado MC, Calhoun DA. Resistant hypertension, secondary hypertension, and hypertensive crises: diagnostic evaluation and treatment.Cardiol Clin. 2010; 28(4): 639-654.
18. Papadopoulos DP, Mourouzis I, Thomopoulos C, Makris T, Papademetriou V. Hypertension crisis. Blood Press. 2010; 19(6): 328-336.
19. Marik PE, Varon J. Hypertensive crises: challenges and management. Chest. 2007; 131(6): 1949-1962.
20. Sarafidis PA, Georgianos PI, Malindretos P, Laikopoulos V. Pharmacological menagement of hypertensive emergencies and urgencies: focus on newer agents.; Expert Opin Investig Drugs. 2012; 21(8): 1089-1106.
21. Hirschl MM, Seidler D, Müllner M, Kürkciyan I, Hekner H, Bur A, Laggner AN. Efficacy of different antihypertensive drugs in the emergency department. J Hum Hypertens. 1996; 10 Suppl 3: S143-146.
22. Martin JF, Higashiama E, Garcia E, Luizon MR, Cipullo JP. Hypertensive crisis profile. Prevalence and clinical presentation. Arq Bras Cardiol. 2004; 83(2): 131-136.