

THE ROLE OF ANXIOLYTICS IN HYPERTENSIVE URGENCY MANAGEMENT

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SUMMARY

Current guidelines do not cover hypertensive urgency management in out-of-hospital setting. Main goal of this study was to evaluate the value of anxiolytic therapy in hypertensive urgencies. We analyzed data gathered by out-of-hospital unit set up during one year. Arterial hypertension was the primary diagnosis in 178 (6.11%) patients, of whom 144 had hypertensive urgency with mean SBP reduction 19.5±7.2%; control group 10.1±6.9%. Anxiolytic therapy was administered in 60% of patients in hypertensive urgency group, and they had a statistically significant greater SBP reduction ($p=0.03$) than patients who did not receive anxiolytic therapy. There is a place for anxiolytic therapy in hypertensive urgency management.

Key words: arterial hypertension - hypertensive urgency - anxiolytics - emergency medicine

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INTRODUCTION

Arterial hypertension is defined by chronic elevation of systolic blood pressure (SBP) greater than 140 mmHg, and/or diastolic blood pressure (DBP) greater than 90 mmHg (Williams et al. 2018). Most people who have hypertension have no symptoms at all; this is why it is known as the “silent killer” (Lawes et al. 2008, Prkačin et al. 2017). Current estimates are that about 1 to 2% of patients with hypertension will have a hypertensive crisis at some point in their lifetime (Marik & Varon 2007). Hypertensive crisis is a frequently used term which includes both hypertensive emergency (HE) and hypertensive urgency (HU). Hypertensive emergency (HE) is acute elevation of blood pressure (SBP > 180 mmHg, DBP > 120 mmHg) accompanied by end organ damage primarily in eyes, brain, heart, aorta, kidneys (Williams et al. 2018, Baumann 2016). Hypertensive urgency (HU) is defined as acute elevation of blood pressure above often used arbitrary limit of SBP > 180 mmHg and/or DBP > 120 mmHg, without end organ damage (Baumann 2016). The prevalence of arterial hypertension in general public adults in Croatia is about 37.5% (Kralj et al. 2017). Around 5% of patient visits to the out-of-hospital emergency medical service (EMS) units in Croatia is associated with hypertension, but mostly without hypertensive emergency (Simić et al. 2017). There are no definite guidelines on prehospital management of HE and HU (Williams et al. 2018, Whelton et al. 2018). The treatment of HE is usually carried out in hospital intensive care units with intravenous antihypertensive agents (Prkačin et al. 2017,

Varon 2008). Guidelines recommend reduction of SBP by no more than 25% within the first hour, and then gradual reduction to normal SBP over the next 24 to 48 hours. On the other hand HU may in general be treated with oral antihypertensives as an outpatient, and the target BP should be achieved over hours to days (Rodriguez et al. 2010, Cherney & Straus 2002). It is well understood that emotional reactivity and anxiety is associated with increased risk of hypertension where support management of anxiety is crucial in hypertensive patients (Ifeagwazi et al. 2017, Pan et al. 2015). HU can also be treated with a variety of intravenous agents, only urapidil is available in some Emergency medicine institute (EMS) (Cherney & Straus 2002). Our main goal was to assess the value of anxiolytic agents in management of hypertensive urgency.

SUBJECTS AND METHODS

We analysed data from the medical records of the EMS unit set up in Community Health Center in town of Sveti Ivan Zelina, branch of Institute for Emergency Medicine of Zagreb County, for a period of one year, from December 2016 to November 2017. The study was submitted to and approved by the Committee on Ethics and Research of the institution. In the above mentioned period a total of 2912 patients were treated in EMS unit set up in the community health center and in 178 (6.11%) cases the primary diagnosis was arterial hypertension. Records from field interventions or interventions at patient home were not included in the research. Severely hypertensive patients with acute end-organ

damage that meets the criteria for hypertensive emergency have been excluded from the research because their primary diagnosis was classified according to the end-organ damage. Patient without two blood pressure measurements or recorded times of those measurements were also excluded. A total of 144 patients met all the criteria for this study, 44 men and 100 women. The first group consisted of 52 patients with AH, but without HU, and the second one consisted of 92 patients with the criteria for HU (SBP above 180 mmHg and/or DBP above 120 mmHg). The analyzed data included from the record were; sex, age, therapy 6 hours prior to pre-hospital EMS unit admission, blood pressure upon pre-hospital EMS unit admission, therapy applied, control blood pressure measurements after the applied therapy, time from first to last measurement, referral to Integrated hospital emergency admission units, home or to the GP. All of the medications were given orally, with exception of urapidil which was administered intravenously. Patients in the control group most commonly received the following medications: AT + nitrate combination (15%); nitrate + benzodiazepine (13%); benzodiazepine (13%). It should be noted that 35% of patients in that group did not receive any medication therapy. Descriptive analysis was performed for qualitative variables and quantitative results are presented as means and standard deviation.

Statistical analysis

Kolmogorov-Smirnov test was used to determine the normality distribution of the tested parameters. None of the tested parameters showed normal distribution, therefore Mann-Whitney U test was used to determine the significance of our results. To compare qualitative variables χ^2 test and Fisher's exact test was used depending on the sample size. Analysis of the data was performed by the statistical program IBM SPSS® software version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

There was no difference in the proportion of subjects in the control and HU group in relation to sex (67%vs 71% of women, $p>0.05$). Patients with a hypertensive urgency had a greater mean age ($59\pm 15y$ vs $67\pm 11y$, $p=0.02$). First measured systolic blood pressure in control group was 162 ± 11 mmHg and last measured was 145 ± 9 mmHg. In the HU group first measured systolic blood pressure was 197 ± 15 mmHg and last measured was 158 ± 18 mmHg. There was no statistical significance among the groups in the number of patients who received medicines at home prior to arrival to EMS unit. (40% vs 43%, $p=0.718$). Patients with hypertensive urgency had longer periods of time between the first and the last blood pressure measurements (26 ± 11 min vs 34 ± 17 min, $p=0.017$). Of the 92 patients treated in the HU group 13 were referred to the Integrated hospital admission unit. Patients from the HU group were more frequently referred to the hospital (4% vs 14%, $p=0.052$). Differences in blood pressure reading between groups in relation to applied therapy are shown in table 1. The most significant drop in SBP ($17.7\pm 5.0\%$) was recorded with patients that received the AT + nitrate + benzodiazepine combination. The mean of the SPB decrease percentage regardless of a therapeutic choice was $10.1\pm 6.9\%$. Patients in the hypertensive urgency group received: AT + nitrate combination (28%); nitrate (18%), nitrate + benzodiazepine (16%); AT + nitrate + benzodiazepine (14%). Unlike the control group 5% of patients in hypertensive urgency group received urapidil as monotherapy. The biggest drop in SBP ($23.6\pm 3.9\%$) was recorded with patients that received the nitrate + benzodiazepine combination. AT as the only administered medication was the least aggressive option with $14.1\pm 5.0\%$ drop in SBP values during the follow-up. Anxiolytic of choice was diazepam.

Table 1. Differences in blood pressure reading between groups in relation to applied therapy

	Patients with AH* without HU**			Patients with HU**		
	Number of patients	Percentage in the group	Percentage of the SBP*** drop	Number of patients	Percentage in the group	Percentage of the SBP*** drop
Without treatment	18	35%	7.3±7.8%	1	1%	0
Antihypertensive	3	6%	4.2±3.7%	7	8%	14.1±5.0%
Nitrate	4	8%	12.1±2.0%	17	18%	17.9±6.3%
Anxiolytic	6	12%	9.0±1.9%	4	4%	20.1±7.7%
Antihypertensive + nitrate	8	15%	13.9±7.0%	26	28%	19.4±8.3%
Nitrate + anxiolytic	7	13%	12.3±5.0%	15	16%	23.6±3.9%
Antihypertensive + anxiolytic	2	4%	4.3±6.1%	4	4%	17.5±8.0%
Antihypertensive + nitrate + anxiolytic	4	8%	17.7±5.0%	13	14%	21.5±4.6%
Urapidil	0	0%		5	5%	19.7±9.8%
Overall	52	100%	10.1±6.9%	92	100%	19.5±7.2%

*AH - arterial hypertension; **HU - hypertensive urgency; ***SBP - systolic blood pressure

Overall 37 patients with HU received diazepam, either as monotherapy or in combination with other medications (anxiolysis group), compared with 55 patients which were treated without diazepam (control group). Patient demographics (age and sex) and initial SBP were similar between the two groups. The SBP reduction was greater in the anxiolysis group, it was $21.9\% \pm 5.2\%$ of initial SBP, compared to the control group ($17.9\% \pm 7.9\%$) ($p=0.03$). The comparison of patient referral to Integrated hospital emergency admission unit revealed a significantly infrequent referral in anxiolysis group ($p=0.013$). Only 1 (3%) patient from the anxiolysis group was referred for additional hospital care, compared to 12 (22%) patients from the control group.

DISCUSSION

In an out-of-hospital environment observation of the patient for a long time is not possible which results in more aggressive treatment. Because the primary health care and family doctor service is poorly organized, due to many factors, patients tend to switch to those services that are more accessible, which leads to over using EMS. Consequently, medical conditions for which an emergency medical service utilization can be considered avoidable are overrepresented (Kostanj et al. 2014). Arterial hypertension is one of the main risk factors for morbidity and mortality worldwide (Williams et al. 2018). Approximately 40% of the population older than 25 has high blood pressure, which accounts for around one billion people, and at least 1 % of those patients will develop hypertensive crisis (Rodriguez et al. 2010, Kralj et al. 2017). Use of anxiolytics in hypertensive urgency in our data analysis has shown to be useful. Despite lowering the SBP more ($-21.9\% \pm 5.2\%$ vs. $-17.9\% \pm 7.9\%$; $p=0.03$), the variability of the SBP lowered is more predictable in the anxiolytic group. Also, less patients were referred to the Integrated hospital emergency admission units that received benzodiazepines (3% vs. 22%; $p=0.013$). These finding could be a result of individual assessment of the physician on duty. An interesting fact to point out is that none of the AH used during the research have a time of onset shorter than an hour, except the nitrate group, and average follow-up time was 34 ± 17 minutes. Nevertheless, significant SBP drops have been reached even in the groups where nitrates were not used nor did the patients take their therapy 6 hours before their visit to the EMS unit. One of the possible explanations is that a comforting dialogue, placebo effect of the antihypertensive medicine taken and anxiolytics have a much larger role in HU management than presumed.

We have to think than many patients in an EMS with acute pain or distress may experience an acute elevation

in BP that will be restored to normal when the pain and distress are relieved. Choosing the right antihypertensive therapy and dosage for a patient with HU is a challenge for every EMS physician, especially in an out-of-hospital environment. Anxiolytic therapy in HU treatment has important place. A unified approach doesn't exist and every patient needs to be assessed individually, however structured approach through some form of guidelines, especially designed for out-of-hospital environment could provide benefit for patients.

CONCLUSION

Due to working conditions and patient expectations, out-of-hospital EMS physicians are more inclined to take a more aggressive approach to lowering blood pressure; but despite this they continue to comply with the general guidelines. Anxiolytic therapy in HU treatment should have its place. However, further investigations must be made for a definite conclusion.

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Contribution of individual authors:

Frane Paštrović: study design, literature review, first draft, writing the manuscript;

Petar Krešimir Okštajner: study design, first draft, writing the manuscript;

Marko Vodanović: statistical analyses, approval of the final version;

Dominik Raos: study design, first draft, writing the manuscript, statistical analyses;

Juraj Jug: writing the manuscript, approval of the final version;

Martina Lovrić Benčić: approval of the final version;

Ingrid Prkačin: writing the manuscript, approval of the final version.

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