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EVALUATION OF ANTIHYPERTENSIVE DRUGS IN PEDIATRIC POPULATION

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ABSTRACT
Prevalence of pediatric hypertension is rising, primarily because of concomitant rise in the prevalence of obese children. Pediatric hypertension represents child's blood pressure greater than 95th percentile in respect to age, gender and height. **Aim: Matherials and Methods:** The study was designed as an observational, analytical, cohort study. It took place from February to July 2015 at the Pediatric Clinic CCU Sarajevo's Department of Cardiology and included a total of 82 patients. **Results and Discussion:** The most important parameters investigated were measurements of blood pressures in 3 therapeutic groups – patients implementing hygienic-dietetic regimen, patients solely on drug therapy, as well as patients on combined therapy (drug therapy and hygienic-dietetic regimen) – collected through measurements using sphygmomanometer and 24h ambulatory blood pressure monitoring. Most commonly used drugs were angiotensin converting enzyme inhibitors, beta-blockers, diuretics and calcium channel blockers. **Conclusion:** Implementing hygienic-dietetic regimen, drug therapy, as well as combined therapy leads to normalisation of blood pressure in children, and can prevent the progress of pediatric hypertension into adulthood.

KEYWORDS: Hypertension, pediatric population, drug therapy.

INTRODUCTION
Pediatric hypertension has become a major health issue – firstly, the prevalence of hypertension is increasing[1] and is approximately 6.9%; secondly, hypertension eventually leads to end-organ damage, which contributes to mortality and morbidity later in life; finally, pediatric hypertension persists throughout adulthood – and this further complicates things, seeing as hypertension is one of many cardiovascular risk factors responsible for development of atherosclerosis, coronary artery disease and cerebrovascular disease.[2] In most patients, first line treatment consists of lifestyle changes, including specific dietary changes and regular exercise[3] – this is of considerable benefit to obese patients.[4] Next step includes drug therapy, with most commonly used drugs being angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs or sartans) and calcium channel blockers (CCBs).[5] By reviewing available literature, it was concluded that ***no specific*** therapeutic algorithm exists for management of pediatric hypertension. Moreover, a systematic review of the effects of antihypertensive drugs in children is yet to be implemented[6], although there are a number of studies in which efficacy of different groups of antihypertensive drugs was determined, as well as their safety profiles – but these will be mentioned below.

The primary aim of this study was assessing the efficiency of different therapeutic approaches to managing pediatric hypertension. Patients were divided into 4 groups depending on the therapeutic regimen and effects of those regimens were investigated by comparing blood pressure measurements taken on two separate occasions. We also gathered data to get a more concrete picture of the prevalence of hypertension according to age and gender, the presence of certain cardiovascular risk factors (especially obesity) and co-morbidities. Finally, we wanted to find out which drugs are most commonly used for hypertension and see if those were according to current recommendations.

MATERIALS AND METHODS

The study was designed as an observational, analytical, cohort retrospective study. It took place from February to July 2015 at the Pediatric Clinic CCU Sarajevo's Department of Cardiology. Data was collected by searching through medical records of patients hospitalized from April 2013 to April 2015. In the end, the study consisted of 82 patients with diagnosed hypertension, but control data was only available for 35 patients. Inclusion criteria included patients who were hospitalized on the Pediatric Clinic CCU Sarajevo from April 2013 to April 2015, patients with a confirmed hypertension diagnosis and availability of control data on blood pressure levels prior to and following assigning a certain therapeutic regime. The collected data was presented using tables and graphs, which included absolute and relative number of cases, arithmetic mean with standard deviation and values range. Chi-square test and analysis of variance (ANOVA) were used to test differences and deviations in expected distribution, with level of significance set to p<0,05 or reliability index 95%. Data was analyzed using IBM Statistics SPSS v 21.0 statistical package.

RESULTS

This study consisted of 82 patients, all of whom conformed with the above mentioned inclusion criteria.

Table 1. ***Patient structure by gender.***

Gender	Number of patients	%
Female	24	29,3
Male	58	70,7
Total	82	100

$\chi^2=13,28$; *df=1; p=0,0002.*

Total number of patients was 82, with 24 female – 29.3% and 58 male patients – 70.7%. Using the chi-square test it was found that there was a statistically significant difference between male and female patients (P<0, 05).

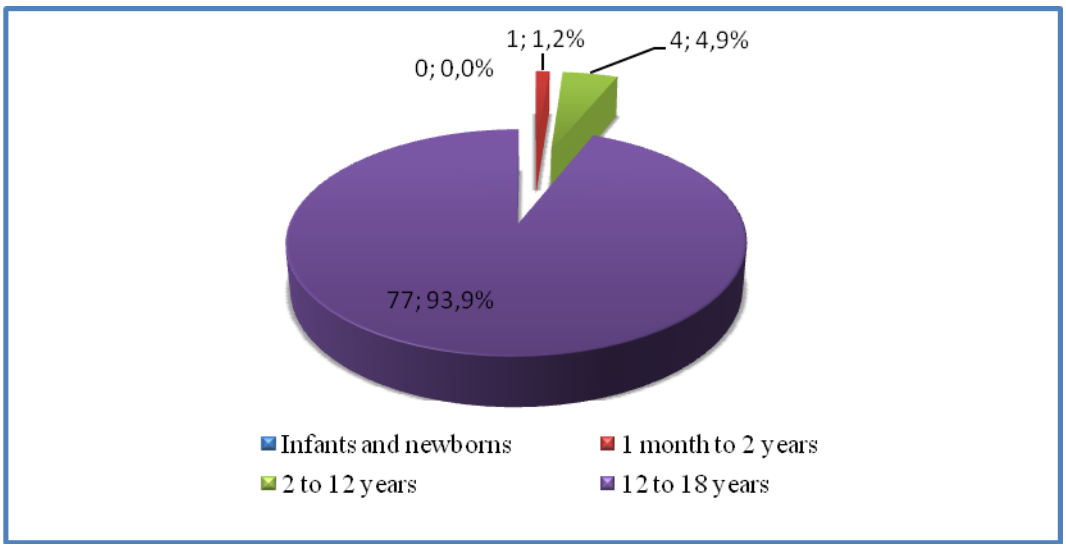

chart 1. ***Patient structure by age.***

Most patients were aged 12 to 18 – 77 of them (93.9%). In the infants and newborns age group, there were no patients, with only one patient in the age group 1 month to 2 years and 4 patients (4.9%) belonging to age group 2 to 12 years. There was a statistically significant difference in the distribution of patients, with most patients in the eldest age group (P<0, 05).

Most commonly used antihypertensive drugs with a comparison between dosage in children and adults

Table 2. ***Most commonly used antihypertensive drugs in relation to different drug classes.***

No	Class of drugs	Total number of patients using specific class of drugs	%
1.	Angiotensin converting enzyme inhibitors (ACEIs)	40	**71,4**
2.	Diuretics	2	**3,6**
3.	Beta-blockers	3	**5,3**
4.	Calcium channel blockers	2	**3,6**
5.	Angiotensin II receptor blockers (ARBs)	1	**1,8**
6.	ACEIs + thiazide diuretic	7	**12,5**
7.	ARBs + thiazide diuretic	1	**1,8**
8.	**Total number of patients on drug therapy**	**56**	**100**

Most commonly used drug class were ACEIs with a percentage of 71.4% (40 patients), followed by combination of an ACEI and thiazide diuretic (12.5%), bewta-blockers (5.3%), calcium channel blockers and diuretics (3.6%). Least used antihypertensive drugs belonged to the class of ARBs, with a percentage of 1.8%, followed by a combination of an ARB and thiazide diuretic (also 1.8%).

Table 3. ***Prescribed drug therapy in the designated sample.***

No	Generic name	Class of drugs	Recommended dosage and application	Recommended dosage and application in adults	Percentage of patients
1.	Enalapril	ACEIs	Initial dose 2,5 mg/day, titrated further according to the results of ABPM*; maximum dose 10 mg/day	Initial dose 5 mg/day, Maintenance dose 20 mg/day 1-2x1	**67,9**
2.	Enalapril + hydrochlorothiazide	ACEIs + thiazide diuretic	10 mg 1-2x1	20 mg 1x1, atypically 2x1	**10,7**
3.	Losartan	ARBs	50 mg 1x1	50 mg 1x1	**1,8**
4.	Losartan + hydrochlorothiazide	ARBs + thiazide diuretic	50 mg 1x1	50 mg 1x1	**1,8**
5.	Ramipril	ACEIs	1.25 mg 2x1	Initial dose 1,25-2,5 mg/d,	**1,8**
6.	Lisinopril	ACEIs	5 mg, according to following dosing scheme 1+1/2+0	Initial dose 2,5 mg/d, maintenance dose 10-20 mg/d, maximum 80 mg/d	**1,8**
7.	Lisinopril + hydrochlorothiazide	ACEIs + thiazide diuretic	10 mg 1x1	10 mg 1x1	**1,8**
8.	Verapamil	Calcium channel blockers	40 mg 2x1	120-160 mg 2-3x1	**1,8**
9.	Nifedipine	Calcium channel blockers	10 mg, 3x1/2	20 mg 2x1, max 40 mg 2x1	**1,8**
10.	Metoprolol	Beta-blockers	50 mg, 2x1/2	100 mg 1x1	**1,8**
11.	Propranolol	Beta-blockers	40 mg 2x1/2	80 mg 2x1	**1,8**
12.	Atenolol	Beta-blockers	50 mg 1x1	25-50 mg 1x1	**1,8**
13.	Spironolactone	Potassium-sparing diuretics	3 mg 2x1	50-100 mg 1x1	**1,8**
14.	Furosemide	Loop diuretics	3 mg 2x1	40 mg 1x1 every second/third day or 20 mg every day	**1,8**
***ABPM – 24 h ambulatory blood pressure monitoring**					

Majority of patients used **enalapril** (67.9%), while 10.7% of the patients used combination of enalapril and hydrochlorothiazide. When comparing the dosage of drugs in children and adults, it can be seen that the prescribed doses in adults were higher for calcium channel blockers, spironolactone and furosemide, whereas other drugs' doses were similar to those used in children.

Patients were divided into 4 groups as seen in *Table 4.* and most of the patients were in the drug therapy group (18 patients or 51.4%). Four patients were solely on hygienic-dietetic regimen (11.4%), 10 were on a combined regimen (28.6%), with three more patients without any therapeutic regimen (8.6%). There was a statistically significant deviation from expected distribution, with more patients in the drug and combination therapy groups ($P < 0,05$).

Table 4. ***Patient groups according to specific therapeutic regimen.***

Therapeutic regimen	Number of patients	%
Hygienic-dietetic regimen	4	**11.4**
Drug therapy	18	**51.4**
Drug therapy + hygienic-dietetic regimen	10	**28.6**
Without therapeutic regimen	3	**8.6**
Total	**35**	**100**

$\chi^2=16,314$; df=3; p=0,0009.

Evaluation of efficacy was done by comparing absolute values of systolic/diastolic blood pressure measurements taken initially and on the following visit - using both sphygmomanometer and ABPM values.

Comparing the absolute values of systolic blood pressure at two visits, the greatest reduction was seen with hygienic-dietetic regimen (26.7%), followed by combination of pharmacotherapy and HD regimen (22.06%) and least reduction with solely pharmacotherapy (0.76%). There was a statistically significant difference among different regimens ($p<0,05$). When comparing the absolute values of diastolic blood pressure, the results showed greatest reduction of diastolic blood pressure with hygienic-dietetic regimen (27.5%), followed by combination therapy (22.02%) and solely pharmacotherapy (1.5%).

In respect to values obtained using mercury sphygmomanometer, the greatest reduction in systolic blood pressure was in the HD regimen group (-5.75 mmHg), followed by combined therapy (-4.44 mmHg) and pharmacotherapy (- 3.95 mmHg). There was no statistical significance among different therapeutic regimens ($p>0,05$). The greatest reduction of diastolic pressure in respect to values obtained by sphygmomanometer was with the combined regimen (-8.6 mmHg), followed by pharmacotherapy (-0.83) and HD regimen (-0.63 mmHg), with a statistical significance among different regimens ($p<0,05$).

DISCUSSION

The results of our study showed that all three therapeutic regimes essentially lead to reductions in systolic and diastolic blood pressure. However, according to our study, the best therapeutic regimen was hygienic-dietetic regimen - this regimen was especially good at lowering systolic blood pressure compared to the other two regimens. On the other hand, values of systolic and diastolic blood pressures were only slightly reduced in patients solely on drug therapy. Patients on combined regimen showed modest reduction in systolic blood pressure, but superior reduction in diastolic blood pressure.

The hygienic-dietetic regimen is indeed an awesome tool to be used by clinicians when treating their patients - no matter "big or small". For example, there is a lot available data and gudelines[3, 7, 8, 9] that clearly portray this - regular exercise can reduce systolic and diastolic blood pressure by 1 and 3%, respectively. Likewise, weight regulation reduces both systolic and diastolic blood pressure – losing 5.1 kg reduces systolic and diastolic blood pressure by 4.4 mmHg and 3.57 mmHg, respectively.[10] Also, a very important detail - the so-called "reduced sodium intake" diet reduced 24-hour values of systolic blood pressure by 11.5 mmHg and diastolic by 5.5 mmHg.[11] Moreover, some data suggest that adding potassium and calcium supplementation in children with salt sensitivity has a benefit on reducing blood pressure.[12] Other[14,15] a diet rich in fibers with low content of saturated fats, cholesterol and refined sugars and avoiding risk factors such as cigarette smoking and alcohol. This is only logical, notably in primary hypertension, which is thought of as a multifactorial disease influenced by both genetic[13] and environmental factors - proper adherence to recommended diet and exercise plan will influence this "half-side" of hypertension.

Limited number of studies – most of which are reviewed in an article from 2014[16] – found that antihypertensive drugs had modest effects on both systolic and diastolic blood pressure, but were generally well tolerated and safe. However, since most studies were short-term, none showed whether drug therapy had effects on long-term outcome for children. On the other hand, results of several studies showed that drug therapy is actually effective in lowering both systolic and diastolic blood pressure – namely, enalapril was showed to be highly effective and well-tolerated[17], as well as lisinopril[18] and losartan.[19] It is important mentioning that losartan had a better reducing potential for diastolic, than for systolic blood pressure.

As mentioned earlier, effects of drug therapy in our study were modest – eventhough most patients used prementioned „highly effective“ enalapril, reductions were still slight. This however can be influenced by multiple factors – noncompliance with the therapy, general therapy refusal, subtherapeutic dosage of drugs or poor therapy tailoring. It is also possible that patients were caught in a „transitory“ period, because drug therapy takes some time to have a full effect (approximately 4 to 8 weeks). There is a possibility that the practising pediatrician was not familiar with drug therapy protocols or how to monitor the effects of the therapy. It should also be noted that socio-economic status influenced the results – some parents are maybe unable to provide their children with the prescribed medications or even take their children for regular blood pressure check-ups.

Other various parameters were investigated in order to get a more concrete picture of pediatric hypertension, and some of these are important in the sense that they can help us further therapeutic approaches to this problem. For example, we found that chief part of patients were ***obese*** – almost third of them! This is according to the results of other studies[20, 21] and is crucial because these patients, although having an increased risk for development of cardiovascular and cerebrovascular disease[22], can be „co-treated“ with proper diet and exercise. Knowing that the prevalence of hypertension is progressively increased with increase in body mass index (BMI) and that 30% of obese children have hypertension[23], one can easily perceive the benefits of addressing obesity problem early on. Another finding worth mentioning is that the most widely used group of antihypertensive drugs were ACEIs, followed by beta-blockers and calcium channel blockers/thiazide diuretics. In a study from 2012[24], results showed that 26% of patients used ACEIs, 20% diuretics and 17% used beta-blockers. 28% of adolescents were prescribed with a combined pharmacotherapy involving more than

one drug, with following combinations being most common: an ACEIs + thiazide diuretic, beta-blockers + thiazide diuretic and diuretic + diuretic.

The limitations of our study were as follows:

1) Methodological limitations:

a. Small sample size, which made it difficult to find significant relationships from data;
b. Lack of available control data for all the patients, which further reduced the data needed for proper evaluation of the regimes; this also impacted the time needed to collect all the data prolonging the duration of the study;
c. Lack of similar studies concerning this particular topic or at least lack of studies with similar design as ours;
d. Lack of direct contact with the patients and direct data collection, which definitely would be time-consuming, but would boost the accuracy of the results.

CONCLUSION

The results of our study will shed some light on the importance of properly implementing hygienic-dietetic regimen, drug therapy, as well as combined therapy that can lead to normalisation of blood pressure in children, and can prevent the progress of pediatric hypertension into adulthood.

In the future, we hope for more studies concerning the problem of antihypertensive therapy in children. Most importantly, studies are needed to evaluate long-term effects of antihypertensive therapy, as well as the success of such therapy in preventing the development of hypertension complications.

The results of our study will help direct future management recommendations and stress the importance of early detection and appropriate treatment of pediatric hypertension, along with the other factors that lead to cardio- and cerebrovascular disease.

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