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CHOICE OF ANTIHYPERTENSIVE THERAPY IN HYPERTENSIVE PATIENTS WITH CRITICAL CORONARY ARTERY STENOSIS

ВЫБОР ГИПОТЕНЗИВНОЙ ТЕРАПИИ У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ НА ФОНЕ КРИТИЧЕСКОГО СТЕНОЗА КОРОНАРНЫХ АРТЕРИЙ

Abstract

Sixty patients with stages II-III AH were studied. ABPM was performed in all the patients. DBPP was assessed by the degree of nocturnal BP lowering. Patients were randomized into groups receiving perindopril or losartan potassium. Perindopril was prescribed at a dose of 4 mg/day with subsequent rising up to 8 mg/day during 7 days. The initial dose of losartan potassium was 25 mg with subsequent rising up to 50 mg 2 times a day. The duration of observation was 8 weeks. Thus, perindopril therapy in hypertensive patients in the preoperative CABG period increased the number of people with normal BP profile.

Key words: arterial hypertension; blood pressure; ambulatory blood pressure monitoring; perindopril; losartan potassium; coronary artery bypass grafting.

Аннотация

Проведено исследование 60 больных 3 стадии АГ. Пациентам проведено суточное мониторирование артериального давления с оценкой суточного профиля АД по степени снижения ночного АД. Обследованные больные были рандомизированы в группы получавшие периндоприл и лозартан калия. Периндоприл назначали в дозе 4 мг/сут с последующей титрацией дозы до 8 мг/сут в течение 7 дней. Стартовая доза лозартана калия составила 50 мг/сут с последующей титрацией до 100 мг/сут в два приема. Длительность исследования составила 8 недель. В нашем исследовании установлено, что у больных гипертонической болезнью в предоперационном периоде АКШ назначение периндоприла приводит к увеличению количества пациентов с нормальным профилем АД.

Ключевые слова: артериальная гипертензия, артериальное давление, амбулаторное мониторирование артериального давления, периндоприл, лозартан калия, аортокоронарное шунтирование.

Introduction. Arterial hypertension (AH) remains one of the most significant non-communicable pandemics in human history, determining the structure of cardiovascular (CV) disease and mortality. Moreover, prolonged elevation of arterial blood pressure (BP) causes myocardial remodeling with worsening perfusion, accelerating of atherosclerotic processes in the arteries. Thus, the latter leads to the development of ischemic heart

disease (IHD), cardiosclerosis and heart failure [1]. Target organ damage including the heart and blood vessels in hypertensive disease is determined by the presence of AH. But in its turn it correlates more closely with ambulatory blood pressure monitoring (ABPM) parameters, such as high absolute values, variability during the day as well as blood pressure load [2]. Additionally, the target organ damage is associated with circadian rhythm of BP.

Based on these reasons, the goal of therapeutic effects should be in achieving the target BP less than 140/90 mm Hg as well as desensitization of resistive type arteries to presser effects. Taking this into consideration, among antihypertensive drugs the preference should be given to the use of inhibitors of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (APA) which have great opportunities to correct BP level [3].

Unlike thiazide derivatives and beta-blockers with negative effect on the development of atherosclerosis and diabetes, ACE inhibitors and ARA represent a class of antihypertensive drugs with metabolically neutral effect [4, 5], improving endothelial function [6], as well as restoring the balance between vasopressor and vasodilator systems [7]. In fact, the use of these antihypertensive drugs for effective control of BP as monotherapy is another important aspect of these groups of drugs. The use of monotherapy for reaching target BP has many advantages, especially in terms of adherence to therapy as well as achieving the optimum control over treatment. These drugs are also recommended for reduction in CV mortality, nonfatal myocardial infarction, and stroke, as well as the need for coronary angioplasty or coronary artery bypass grafting (CABG) [8].

IHD and cerebral stroke are most frequent among CV diseases occurring in patients with AH. AH and concomitant ischemic heart disease increase the risk of morbidity and mortality twofold and fall under a very high risk category by Framingham criteria (USA) and SCORE (European Society of Cardiology) regardless of BP. Cerebral vascular events in patients who underwent CABG as well as higher incidence of neurological disorders (0.4% to 80%, depending on the diagnostic method) present a significant problem in cardiology, as hypertension is considered to be one of the major causes of postoperative stroke and encephalopathy after CABG [9].

ABPM gives the opportunity to reveal and identify changes of diurnal BP profile (DBPP) of both in terms of detection of high absolute values and variability of degree of nocturnal BP lowering and pressure load. Direct evidence of pathological morning BP raise results in increasing mortality from CV causes. Today the problem of choice of antihypertensive medications affecting DBPP is still challenging.

Objective. A comparative analysis of perindopril and losartan potassium effect in patients with III stage hypertensive disease on ABPM parameters in order to evaluate antihypertensive effect of these drugs in patients before CABG.

Materials and Methods. Sixty patients with III stage hypertensive disease after myocardial infarction (in more than 6 months before CABG) with stenotic coronary atherosclerosis (confirmed by coronary angiography) were reviewed. The present study was approved by the Ethical Committee and all patients gave informed consent. The exclusion criteria of the study were: rhythm disturbances in the form of frequent ventricular and supraventricular extra systoles (more than 6/ min), permanent atrial fibrillation; concomitant severe liver diseases, kidney, respiratory organs with respiratory failure, as well as cancer. All patients underwent routine clinical, laboratory and instrumental examination including physical examination, biochemical blood tests, urinalysis, electrocardiography, and ABPM.

Ambulatory BP monitoring was performed by means of AVRM-04 Recorder («Meditech», Hungary). Average levels of systolic BP (SBP), diastolic BP (DBP) and heart rate were measured during 24 hours. The time index was defined as the percentage of

BP measurements, during which BP level exceeded its threshold (140/90 mm Hg for wake hours and 120/80 mm Hg for night time). BP variability was calculated as standard deviation of 24 h SBP and DBP, daytime and nighttime separately. The diurnal profile was assessed by the degree of nocturnal BP lowering, and is defined as the ratio of the difference between the average values of BP during awake and sleep hours to the average daytime BP values expressed in percentage. Values more than 10% and less than 20% were taken as normal BP dipping. Concomitant therapy included antianginal (nitro agents) and antiplatelet agents (acetylsalicylic acid, 100 mg / day).

Thus, for routine antihypertensive therapy after ABPM all the patients were randomized into groups receiving perindopril (Perineva, KRKA) or losartan potassium (Losap, Zentiva). Perindopril was administered at a dose of 4 mg/day with subsequent rising up to 8 mg/day for 7 days. The initial dosage of losartan potassium was 25 mg with subsequent increasing up to 50 mg 2 times a day (after 7 days of therapy). The duration of observation was 8 weeks. Inefficacy in therapy was a reason for the exclusion of patients from the study and appointment of a combined therapy. Thus, the frequency of achieving target BP (< 140/90 mm Hg) was 61%.

Statistical analysis of the results was performed using the statistical package Statistica 6.0 (Statsoft Inc.). The data are given as Medians [25%; 75%] (Me [Me (n)-Me (b)]). In comparison of the non-normally distributed variables, the Mann-Whitney test was used to test the differences between two groups. For all normally distributed variables, the t-test was used for comparison between two groups. For correlation analysis, Pearson correlation coefficient and Spearman rank correlation coefficient were calculated. Scheffe method of linear contrasts was applied to detect all possible contrasts in individual groups as well as Fisher exact test – while comparing the frequency of adverse changes in the CV system [10].

Results of the study.

The average age of the patients was 56 (50; 60). Distribution of the patients according to the stage of hypertension and the presence of comorbidities and complications are presented in Table 1.

Table 1

Clinical characteristics of patients with AH

Indicator	Perindopril	Losartan potassium
	n=35	*n=25*
Age, years Me [25%; 75%]	54 (50; 60)	58 (51; 60)
AH duration, years	8.0 (5.0; 16.0)	12.0 (8.0; 16.0)
AH stage:		
Stage II Hypertension	23 (65.7%)	15 (60.0%)
Stage III Hypertension	12 (34.0%)	10 (40%)
I FC CHF	12 (34.3%)	13 (52.0%)
II FC	15 (42.8%)	7 (28.0%)
III FC	8 (22.9%)	5 (20.0%)

A comparative analysis of the ambulatory monitoring of BP parameters in patients treated with perindopril and losartan potassium showed the following results (Tab. 2, 3). Perindopril treatment reduced 24-hour and daytime SBP by 17.2% ($p<0.0001$) as compared to baseline, as well as nighttime BP – by 22.5% ($p<0.0001$). At the same time 24-hour and daytime DBP

reduced by 18.3% and 17.6% (p<0.0001), respectively, whereas night DBP decreased by 27.2% (p<0.0001) as compared to baseline.

Thus, the pulse pressure and BP variability (VBP) of both systolic and diastolic were more significant at night, a decrease for SBP was 26.7% (p = 0.004) and 20.0% (p = 0.045) – for DBP. This was accompanied by decrease in the number of non-dippers by 24.3% and night-peakers by 5.4%, as well as increase in number of dippers by 27.0% and over-dippers by 2.7%. Diurnal diastolic pressure also increased due to the group of dippers by 18.9% (p <0.01) and decreased due to non-dippers by 13.5%, night-peakers – by 2.7% as well as over-dippers – by 2.7%.

Table 2

ABPM parameters in the treatment with perindopril and losartan potassium (Me [Me (n) – Me(b)])

Parameters	Group 1 (n =35) Perindopril		Group 2 (n =25) Losartan potassium	
	baseline	*after 8 weeks*	*baseline*	*after 8 weeks*
24-hour SBP	148.0 (139.0; 159.0)	122.5* (118.0; 125.0)	161.5 (144.0; 168.0)	120.0* (120.0; 127.0)°
Daytime SBP	152.0 (143.0; 166.0)	126.0* (122.0; 132.0)	165.0 (150.0; 179.0)	126.0* (115.0; 131.0)
Nighttime SBP	142.5 (132.0; 148.0)	110.5* (107.0; 116.0)	149.0 (134.0; 150.0)	111.0* (108.0; 123.0)
24-hour DBP	90.0 (83.0; 93.0)	73.5* (65.0; 76.0)	99.0 (87.0; 96.0)	69.0* (62.0; 74.0) °
Daytime DBP	94.0 (85.0; 99.0)	77.5* (72.0; 83.0)	95.0 (92.0; 106.0)	73.0* (70.0; 78.0) °
Nighttime DBP	81.0 (73.0; 84.0)	59.0* (57.0; 67.0)	81.0 (77.0; 89.0)	66.0* (52.0; 71.0)
24-hour PBP	63.5 (58.5; 68.5)	48.0* (45.0; 53.0)	69.0 (64.0; 71.0)	52.0* (48.5; 56.0)
Daytime PBP	61.0 (56.0; 65.0)	48.0* (45.0; 52.0)	68.0 (64.0; 73.0)	52.5* (47.5; 54.0)
Nighttime PBP	64.0 (57.0; 71.0)	49.0* (44.0; 53.0)	19.0 (62.0; 68.0)	51.5* (46.0; 57.5)
24-hour SBPV	16.0 (14.0; 19.0)	14.0 (12.0; 16.0)	67.0 (16.0; 25.0)	13.0* (12.5; 16.0) °
Daytime SBPV	15.0 (13.0; 20.0)	12.0 (11.0; 14.0)	13.5 (15.0; 24.0)	13.0 (11.5; 13.5)
Nighttime SBPV	15.0 (13.0; 18.0)	11.0 (9.0; 14.0)	16.5 (12.0; 16.0)	12.0 (10.5; 16.0) °
24-hour DBPV	14.0 (12.0; 16.0)	13.0 (11.0; 14.0)	13.5 (10.0; 18.0)	12.5 (11.5; 13.0)
Daytime DBPV	13.0 (10.0; 15.0)	11.0 (10.0; 13.0)	9.0 (10.0; 15.0)	10.5 (9.0; 11.5)
Nighttime DBPV	10.0 (8.0; 14.0)	8.0 (7.0; 11.0)	12.5 (8.0; 11.0)	10.0 (9.0; 11.0) °

*Notes: ° p<0.04 difference between drugs effect; * p 2-3, 4-5 <0.0001*

Table 3

Diurnal profile of SBP and DBP under the influence of treatment with perindopril and losartan potassium

Diurnal profile	Group 1 (n =35) Perindopril		Group 2 (n =25) Losartan potassium		P (after the atment)
	baseline	*after 8 weeks*	*baseline*	*after 8 weeks*	
1. 24-hour SBP					
Non-dipper	20 (54.1%)	11 (29.7%)*	11 (50.0%)	10 (45.5%)	P=0.027
Dipper	13 (35.1%)	23 (62.2%)*	9 (40.9%)	8 (36.4%)	P=0.002
Night-peaker	3 (8.1%)	1 (2.7%)*	2 (9.1%)	4 (18.2%)*	P=0.011
Over-dipper	1 (2.7%)	2 (5.4%)*	0 (0)	0 (0)	P=0.030
2. 24-hour DBP					
Non-dipper	17 (45.9%)	12 (32.4%)*	10 (45.5%)	9 (40.9%)	P=0.043
Dipper	14 (37.8%)	21 (56.8%)*	8 (36.4%)	10 (45.5%)	P=0.014
Night-peaker	2 (5.4%)	1 (2.7%)	1 (4.5%)	1 (4.5%)	P=0.001
Over-dipper	4 (10.8%)	3 (8.1%)	3 (13.6%)	2 (9.1%)	P=0.032

*Note: * p<0.05 compared with the periods before and after the treatment*

Thus, the effect of perindopril treatment on diurnal rhythm of BP resulted primarily in a decrease in diastolic and pulse BP mostly at night and to a lesser extent in systolic BP, which in its turn led to an increase in the number of patients of dipper type. These changes indicate an improvement in the functioning of vasodilator mechanisms of vascular tone regulation.

The assessment of losartan potassium effect on ambulatory BP monitoring after 8 weeks of therapy showed that 24-hour SBP reduced as compared to baseline by 25.7% (p <0.0001), while daytime – by 23.6% (p <0.0001), nighttime – by 25.5% (p <0.0001). 24-hour DBP reduced by 27.4%, daytime – by 26.3%, night time - by 18.5% (p = 0.003); whereas 24-hour pulse BP significantly reduced by 24.6% (p = 0.0006), daytime – by 22.8% (p = 0.0004) and nighttime – by 23.1% (p = 0.003). The positive dynamics of losartan potassium effect on BP during the day is evidenced by reduction in the values of 24-hour SBPV (up to 31.6%) and daytime DADV (by 16.0%).

A comparative analysis of the hypotensive effect of perindopril and losartan potassium therapy showed significantly much greater changes in VBP in group treated with losartan potassium. Moreover, the number of patients with SBP corresponding to non-dippers maintained at the range of 45.5% in the group treated with losartan potassium that significantly (p = 0.027) differed from the group treated with perindopril. Additionally, a number of dippers for both systolic and DBP significantly increased up to 62.2% and 56.8%, respectively in group treated with perindopril in comparison with losartan therapy.

Thus, a comparative evaluation of the hypotensive effect of perindopril and losartan potassium therapy suggests that reduced DBPP is more preferable in the treatment with perindopril with reduction of VBP during the day. Antihypertensive effect of losartan potassium therapy is more significant in the daytime and nighttime, but it is accompanied by lower 24-hour VBP, although the number of patients corresponding to dippers was significantly less as compared to perindopril therapy.

Discussion of the results. The main goal in the treatment of AH is to minimize the risk of CV complications and death from them [11, 12]. The changes in the circadian rhythm of BP can lead to pathological hypertensive reactions of night peaker, which result in fatal events [13].

Taking this into consideration, BP level lowering as well as an increase in the number of dippers are significant tasks of modern cardiology, which can affect the reduction of cerebral fatal and nonfatal CV events. This applies primarily to ACE inhibitors, such as perindopril [14].

According to some researches, the data of additional cardioprotective properties of ACE inhibitors in IHD patients with AH cannot be explained only by the reduction in BP level. It is estimated that ACE inhibitors affect the basic pathological processes underlying coronary heart disease, such as vasoconstriction, structural changes in the vascular wall as well as left ventricular remodeling. The protective effect of ACE inhibitors on the development of atherosclerosis is possible due to their mechanisms of action. They lead to reducing angiotensin II and increasing the production of nitric oxide and bradykinin as well as improving vascular endothelium functions. One of the mechanisms of anti-ischemic action of ACE inhibitors is peripheral vasodilatation, eliminating the hemodynamic overload of the heart (by both filling and resistance), as well as the reduction of pressure in the ventricles [15]. In our study, we revealed the ability of perindopril to affect the transformation of pathogenic mechanisms of AH (restore circadian BP rhythm violations) by affecting the activity of the renin-angiotensin and related sympathetic nervous systems as well as by improving the vasoregulating endothelial function.

Conclusion. In patients with stage III AH, a significant increase in the average 24-hour, daytime and nighttime BP values, time index, pressure load as well as reduction of nocturnal BP lowering were identified. A high liability of DBPP with high variability was detected, that might be a predictor of acute CV and cerebral events. Thus perindopril therapy in hypertensive patients in the preoperative CABG period increased the number of people with normal BP profile. It is necessary to go on investigating the vascular and neurohormonal mechanisms of pathological remodeling and their relation with the efficacy and safety of antihypertensive therapy with drugs which normalize circadian rhythm of BP that in its turn allows to conduct adequate target correction in time.

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