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RESISTANT HYPERTENSION: PATIENT ADHERENCE TO TREATMENT IN OUTPATIENT SETTINGS

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Introduction. Arterial hypertension is one of the main risk factors for developing fatal cardiovascular complications. Among patients with arterial hypertension, there is a subgroup with therapy-resistant hypertension (RH). Resistant arterial hypertension (RAH) is associated with a 2-6-fold increase in the risk of cardiovascular complications, making the problem of its diagnosis and treatment highly relevant.

Aim. To assess patient adherence to treatment for resistant hypertension conducted in outpatient settings.

Materials and methods. A retrospective analysis of outpatient records of patients with hypertension (n=3 321) was carried out, with observations conducted in 5 polyclinic institutions in the city of Aktobe. A group of patients (n=346) with poorly controlled grade 2-3 hypertension was identified and classified into the RAH group. The effectiveness of combination therapy and adherence to the most used antihypertensive drugs were analyzed.

Results and discussion. Combinations of antihypertensive drugs included in triple therapy did not produce effective results. It was noted that 21.4% of prescriptions consisted of an ACE inhibitor and a beta-blocker + diuretic combination, and 12.7% of cases involved an angiotensin II receptor antagonist (ARA II) + beta-blocker + diuretic. These combinations are no longer considered first-line antihypertensive drug combinations.

Conclusion. The study revealed that the addition of spironolactone to the drug combination led to additional blood pressure reduction in patients with resistant hypertension, thus contributing to improved patient compliance and a more favorable disease course, reducing the risk of frequent complications such as coronary artery disease, acute and chronic brain damage, and kidney disease.

Key words: resistant hypertension; antihypertensive drugs; combination therapy; commitment; in outpatient settings; compliance; spironolactone; beta-blockers

INTRODUCTION:

The problem of arterial hypertension (AH) remains significant worldwide. According to population studies, a substantial portion (up to 40%) of the adult population has elevated blood pressure (BP) [1].

Increased BP is a predictor of complications in cardiovascular diseases — coronary artery disease (CAD), myocardial infarction (MI), chronic heart failure (CHF), stroke, and their adverse outcomes. However, adequate BP control is achieved in only 30-50% of patients in countries with highly developed healthcare systems [1, 2]. Resistant arterial hypertension (RAH) is defined as office blood pressure that remains above the target level despite the simultaneous use of three antihypertensive drugs in optimal doses, one of which is a diuretic [3, 4].

Despite the American Heart Association (AHA) consensus statement emphasizing the importance of RAH, the incidence and prognosis of this condition remain largely unknown [4]. To date, the prevalence of RAH, according to various authors from different countries, ranges from 5 to 20%. These are mainly patients with chronic kidney disease, obesity, diabetes mellitus, left ventricular myocardial hypertrophy, and isolated systolic hypertension [4, 5].

In the analysis of the Spanish blood pressure register (n=70,997), 16.9% of patients had resistant hypertension and 1.35% had refractory hypertension. People with refractory hypertension were more likely to have type 2 diabetes (48.1% *vs* 33.5%; p<0.001), obesity (59.6% *vs* 51.4%; p<0.001), microalbuminuria (38.5% *vs* 24.5%; p<0.0001), left ventricular (LV) myocardial hypertrophy electrocardiography (27.6% *vs* 14.9%; p<0.0001), the history of hypertension was longer (13.9 years *vs* 10.9 years; p<0.0001) and the incidence of cardiovascular complications was higher

Table 1 – Clinical characteristics of patients with hypertension (n=346)

Parameter	Value
Men, n (%)	59 (47.2)
Age, years	58,5±1,08
Duration of Hypertension, years	21,2±0,7
Body Mass Index, kg/m²	31,7±0,6
Systolic blood pressure, mmHg	169±1,15
Diastolic blood pressure, mmHg	95±0,8
Overweight, n (%)	31 (15,7)
Obesity, n (%) grade 1 grade 2 grade 3	34 (17,2) 28 (14,1) 11 (5,6)
Smoking, n (%)	52 (26,3)
Diabetes mellitus, n (%)	38 (19,2)
Chronic pyelonephritis, n (%)	33 (26,2)

(20.5% *vs* 14.9%; p<0.0001) compared with patients with resistant hypertension [6].

Similarities and differences in risk factors for the development of refractory and resistant hypertension were found. Both diagnoses are more common among people of African-American descent. However, refractory hypertension is more common among young people and women [7]. In several studies, when comparing the prevalence of LV hypertrophy assessed by echocardiographic signs, patients with refractory hypertension were more likely to have a higher prevalence of LV hypertrophy than patients with resistant hypertension [8, 9].

In the recent cross-sectional CRIC (Chronic Renal Insufficiency Cohort) study, which included 3367 patients with chronic kidney disease, 40.4% of participants had resistant arterial hypertension [10].

According to a retrospective analysis by M. Acelajado et al. among 304 patients with resistant hypertension observed in a specialized hypertension clinic, only 29 (9.5%) people did not reach the target blood pressure level. In a subsequent prospective analysis in the same clinic, only 3% of the 559 patients initially classified as having uncontrolled resistant hypertension were subsequently diagnosed with refractory hypertension [11].

Among the obvious causes of resistance to therapy, the doctor's choice of a suboptimal treatment regimen and the appointment of irrational drug combinations play an important role; in addition, low patient adherence to therapy becomes an important factor [12].

The aim was to assess patient adherence to treatment for resistant hypertension conducted in outpatient settings.

MATERIALS AND METHODS

Patients with hypertension (n=3 321) was carried out, with observations conducted in 5 polyclinic institutions in Aktobe c. A group of patients (n=346) with poorly controlled grade 2-3 hypertension was identified and classified into the RAH group (Table 1).

Exclusion criteria: previous myocardial infarction, acute cerebrovascular accident in the preceding 6 months, symptomatic hypertension (endocrine and vascular origin), chronic heart failure stage IIA (NYHA class III), tachyarrhythmia. All patients underwent 24-hour BP monitoring before and after the procedure, as well as correction of anti-hypertensive therapy based on the obtained data. Combination therapy for AH consisted of combinations of the following drug groups: beta-blockers, dihydropyridine calcium antagonists, ACE inhibitors, angiotensin II receptor blockers, and diuretics at maximally tolerated doses. At the outpatient-polyclinic stage, BP control was conducted once a month, with analysis of multiple BP measurements and 24-hour BP monitoring after 3 and 6 months.

RESULTS AND DISCUSSION

16.7% of patients received four-component therapy, which included either an ACE inhibitor + β-adreno blocker + calcium antagonist + diuretic (8.7%) or an ARB II + β-adreno blocker + calcium antagonist + diuretic (8%).

Combinations of antihypertensive drugs used in triple-component therapy did not show effective results (Diagram 1). It was noted that 21.4% of prescriptions consisted of the combination of an ACE inhibitor + β-adreno blocker + diuretic, and in 12.7% of

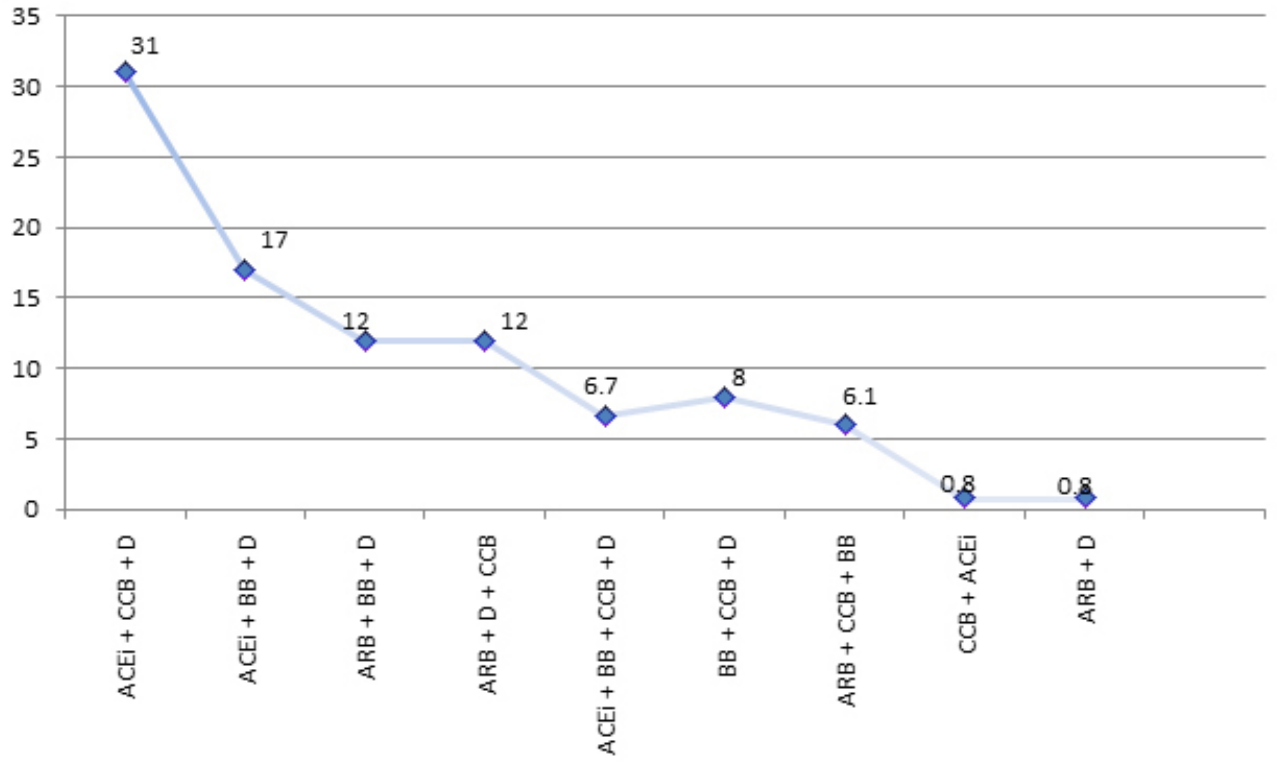

Figure 1 – Frequency of prescription of combination antihypertensive medications (%) (ACEi – Angiotensin-Converting Enzyme Inhibitor; ARB – Angiotensin II Receptor Blocker; BB – Beta-Blocker; CCB – Calcium Channel Blocker; D – Diuretic)

cases — an angiotensin II receptor blocker (ARB II) + β-adreno blocker + diuretic. These combinations are not currently considered first-line antihypertensive drug regimens.

Thus, Figure 1 shows that more than 40% of patients received combinations of drugs. It should be noted that β-adreno blockers were prescribed to 58.6 out of 346 patients (58.1%), among whom 44.6% were patients with hypertension (HTN) combined with stable ischemic heart disease (IHD). At the same time, in 36.5% of patients with HTN without IHD or rhythm disorders, β-adreno blockers were considered by doctors as basic antihypertensive drugs and were included in the complex treatment of patients with resistant arterial hypertension (RAH). This approach naturally led to ineffective blood pressure reduction. Moreover, atenolol was used as the basic agent in 12% of cases among β-adreno blockers. Analysis of drugs from the group of ACE inhibitors showed that ACE inhibitors lacking maximum tissue affinity (e. g., enalapril; Table 2) were used as basic antihypertensive agents. Almost one-third of patients received enalapril. Meanwhile, it is now known that drugs with maximum tissue activity provide a more pronounced organ-protective effect (reducing the risk of adverse outcomes in HTN). Among these, the prescription frequency of perindopril was 93%, while that of quinapril was 0.6%. In the group of patients receiving angiotensin II receptor antagonists, losartan was used by doctors in most cases (45.7%) at ineffective doses for this category of patients (Table 2).

Among calcium antagonists, the dihydropyridine group was the predominant class, with amlodipine prescribed to 96% of patients, nifedipine to 84%, and felodipine to 3.1%. It should also be noted that the dosages of these drugs remained low and, consequently, ineffective. Regarding diuretic therapy, preference was given to indapamide in 78% of cases and hydrochlorothiazide in 43.2% of cases (Table 2).

One of the key requirements in the treatment of resistant hypertension (RH), in the absence of target blood pressure (BP) achievement with triple therapy, is the addition of a mineralocorticoid receptor antagonist such as spironolactone. The effectiveness of spironolactone in RH was demonstrated in a study by Ramsey L.E. et al. Additionally, studies like ASCOT-BPLA and ASPIRANT showed that adding spironolactone to combination therapy results in further BP reduction in patients with RH. Instead of this recommended strategy, doctors opted to use imidazoline receptor agonists (centrally acting drugs) as the fourth drug.

CONCLUSIONS

The treatment of resistant hypertension was carried out using insufficiently effective drug combinations with low doses. Treatment should

Table 2 – Average daily doses and prescription frequency of medications in patients with resistant arterial hypertension (RAH)

Medications	Name	Average Dose (mg/day)	Prescription Frequency (%)
ACEi	Enalapril Perindopril Lisinopril Quinapril	25 8 7,5 15	49,5 93 5,3 0,6
ARB II	Losartan	55	45,7
CCB	Amlodipine Nifedipine Felodipine	5 56 10	96 84 3,1
BB	Bisoprolol Atenolol Metoprolol tartrate	5 80 50	89 12 7,4
Diuretics	Indapamide Hydrochlorothiazide	2,5 20	78 43,2
I1RA	Moxonidine	0,4	0,2

Note: ACEi – Angiotensin-Converting Enzyme Inhibitor; ARB II – Angiotensin II Receptor Blocker; CCB – Calcium Channel Blocker; BB – Beta-Blocker; I1RA – Imidazoline Receptor Agonist

include lifestyle modifications, improved medication adherence, and optimization of drug dosages. Prescribing adequate doses of antihypertensive drugs enhances patient compliance, contributing to a more favorable disease course and reducing the risk of common hypertension-related complications such as ischemic heart disease, acute and chronic brain damage, and kidney injury.

Authors' contribution:

G. Zhakiyeva, E. Nurbaulina – concept and design of the study, collection and processing of materials, writing the original draft, editing, reviewing the final manuscript.

Conflict of interest:

No conflict of interest declared.

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РЕЗИСТЕНТНАЯ АРТЕРИАЛЬНАЯ ГИПЕРТЕНЗИЯ: ПРИВЕРЖЕННОСТЬ ПАЦИЕНТА ЛЕЧЕНИЮ В АМБУЛАТОРНЫХ УСЛОВИЯХ

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Введение. Артериальная гипертония (АГ) является одним из факторов риска развития фатальных сердечно-сосудистых осложнений. Среди пациентов с АГ выделют группу больных резистентной к терапии АГ. Резистентная артериальная гипертония (РАГ) ассоцирована 2-6-кратным увеличением риска сердечно-сосудистых осложнений, в связи с чем проблема ее диагностики и лечения чрезвычайно актуальной.

Цель. Оценка приверженности лечению больных с резистентной гипертензией, проводимой в условиях поликлиники.

Материалы и методы. Проведен ретроспективный анализ амбулаторных карт пациентов с АГ (n=3321), наблюдение которых проводилось в 5 поликлинических учреждениях г. Актобе. Была выделена группа больных (n=346 человек) с трудно контролируемой АГ 2-3 степени, которых отнесли к группе РАГ. Был проведен анализ эффективности комбинированной терапии и приверженностb лечению наиболее часто используемых гипотензивных препаратов.

Результаты и обсуждение. Комбинации антигипертензиных препаратов, входящих в состав трехкомпонентной терапии, не имели эффективного результата. Отмечено, что 21,4% назначений составили комбинации ингибитор АПФ и бета-адреноблокатор + диуретик, и 12,7% случаев – антагонист рецепторов ангиотензин II (АРА II) + бетаадреноблокатор + диуретик. Данные комбинации в настоящее время не являются комбинациями антигипертензивных препаратов первой линии.

Выводы. По результатам исследования выявлено, что добавление к комбинации препаратов спиронолактона приводило к дополнительному снижению АД у пациентов с резистентной АГ, что, соответственно, способствовало улучшению комплаентности больных лечению, и более благоприятному течению заболевания, уменьшая риск развития возможных частых осложнений АГ, таких как ИБС, острые и хронические поражения головного мозга, почек.

Ключевые слова: резистентная гипертония; антигипертензивные препараты; комбинированная терапия; приверженность; амбулаторное лечение; соблюдение режима лечения; спиронолактон; бета-блокаторы

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РЕЗИСТЕНТТІ ГИПЕРТЕНЗИЯ: ЕМХАНА ЖАҒДАЙЫНДА НАУҚАСТАРДЫҢ ЕМДЕЛУІНІҢ НӘТИЖЕЛІЛІГІ

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Кіріспе. Артериялық гипертония өлімге әкелетін жүрек-қан тамырлары асқынуларының негізгі қауіп факторларының бірі болып табылады. Артериялық гипертониямен (АГ) ауыратын науқастар арасында терапияға резистентті АГ бар науқастар тобы ерекшеленеді. Резистентті артериялық гипертония (РАГ) жүрек-қан тамырлары асқынуларының қауіпінің 2-6 есе жоғарылауымен байланысты [2, 3], сондықтан оны диагностикалау және емдеу мәселесі өте өзекті болып көрінеді.

Мақсаты. Емхана жағдайында жүргізілетін резистентті гипертензиясы бар науқастардың емделуінің нәтижелілігін бағалау.

Материалдар және әдістер. АГ (n=3 321) бар пациенттердің амбулаториялық карталарына ретроспективті талдау жүргізілді, олардың бақылауы Ақтөбе қаласының 5 емханалық мекемесінде жүргізілді. РАГ тобына жатқызылған 2-3 дәрежелі АГ бақылауы қиын науқастар тобы (n=346 адам) бөлінді. Аралас терапияның тиімділігіне талдау жасалды және ең жиі қолданылатын гипертензияға қарсы препараттарды емдеуге міндеттеме берілді.

Нәтижелер және талқылау. Үш компонентті терапияның құрамына кіретін гипертензияға қарсы препараттардың комбинациясы тиімді нәтиже бермеді. Тағайындаулардың 21,4% – ААФ ингибиторы мен бета-адреноблокатор + диуретик, ал жағдайлардың 12,7% – ангиотензин II рецепторларының антагонисті (АРА II) + бетаадреноблокатор + диуретик. Бұл комбинациялар қазіргі уақытта бірінші қатардағы гипертензияға қарсы препараттардың комбинациясы болып саналмайды.

Қорытынды. Зерттеу нәтижелері бойынша спиронолактонды препараттардың комбинациясына қосу РАГ бар пациенттерде артериялық қысымның төмендеуіне әкелетіні анықталды, сондықтан ол пациенттердің емдеуге сәйкестігін жақсартуға және аурудың неғұрлым қолайлы ағымына ықпал етті. Мидың, бүйректің жедел және созылмалы зақымдануы сияқты артериялық гипертензияның ықтимал жиі асқынуларының даму қаупін азайтады.

Кілт сөздер: резистентті гипертензия; гипертензияға қарсы препараттар; қосарланған терапия; емге бейімділігі; емхана жағдағында,комплаентілік; спиронолактон; бета-блокаторлар