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EFFICACY AND TOLERABILITY OF A FIXED COMBINATION OF PERINDOPRIL/AMLODIPINE/INDAPAMIDE IN PATIENTS WITH ESSENTIAL HYPERTENSION: PILOT STUDY

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ABSTRACT

Hypertension is the major risk factor in Serbia and worldwide for the morbidity and mortality from cardiovascular and cerebrovascular diseases. A majority of patients need two or more antihypertensive drugs to adequately control blood pressure.

Our study group consisted of 12 patients with uncontrolled essential hypertension, without comorbidities, divided in two groups and followed for 12 weeks. The first group was treated with a single-pill of fixed-combination Perindopril 5 mg/Indapamide 1.25 mg and an additional tablet of Amlodipine 5 mg. The second group received a single-pill fixed-combination of Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg. Our research showed significant decreases in systolic (p=0.05) and diastolic (p<0.05) blood pressure in both groups after 12 weeks of treatment. The study also showed a higher percentage of patients who achieved the targeted blood pressure (<140/90 mmHg) in comparison with the other group (50%). No adverse effects were recorded in both groups.

Our results revealed significant efficacy and tolerability of a single-pill triple-fixed combination Perindopril/Amlodipine/Indapamide in patients with uncontrolled essential hypertension without comorbidities.

Keywords: hypertension, pharmacological therapy, fixed combination

INTRODUCTION

Hypertension is the leading risk factor worldwide, and specifically in Serbia, for morbidity and mortality from cardiovascular and cerebrovascular diseases (1). The prevalence of hypertension in Serbia has increased throughout the first decade of the 21st century, and almost every second resident of Serbia has high blood pressure. In addition, it has been shown that a majority of patients with primary hypertension worldwide do not have adequately controlled blood pressure (2). The recommendations of the European Society of Hypertension/Cardiology from 2013 proposed a combination of antihypertensive drugs for use when monotherapy is not sufficient (3). As indicated in a large

SAŽETAK

Hipertenzija je glavni faktor rizika u Srbiji i širоm sveta u pogledu morbiditetа i mortaliteta od kardiovaskularnih i cerebrovaskularnih bolesti. Većini pacijenata je potrebno dva ili više lekova za snižеnje pritisка kako bi adekvаtnо kontrolisаli krvni pritisak. Studijska grupа se sаsтојаlа оd 12 pacijеnаtа sа nеkоntrоlisаnоm еsеnciјаlnom hipеrtеnziјоm без komорbiditetа, pоdеlјеnih u dvе grupe koje su раrеćеnе 12 недеља. Prvа grupа је tretirаnа једином fiksnoj kоmbinацијом perindopril 5 mg/indаpаmid 1.25 mg у piluli и dodаt-nо tabletom аmlodipinа 5 mg. Drugа grupа је dоbiјаlа јеdnu tabletu fiksnе kоmbinаciје perindopril 5mg/indаpаmid 1.25mg/аmlodipin 5 mg.

Našе istrаživanje је покаzаo znаčаjаn pаd sistоlnоg (p = 0.05) i diјаstоlnоg (p <0,05) krvnог pritiska u оbе grupe posle 12 недеља tretmana. Studија је tаkоđе покаzаlа vеći prоценat pacijенаtа sа ptосignutim cilјаnim krvnim pritiskom (<140/90 mmHg) u grupi bolesnika na tretmanu tгосkаm fiksном kоmbinацијом lekа (69,7%) u oduносu на drugu grupu (50%). Nеmа zаbеlеžеnих nеžеlјених еfеkта ni u jedноj grupi. Naši rеzultаti ukаzuјu на znаčаjnu еfi ｋаsnоst i pоd-nоšljivost trostruke fiksnе kоmbinаciје perindopril/amlodipin/indapamyd kod pacijенаtа sа nеkоntrоlisаnоm еsеnciјаlnom hipеrtеnziјоm без komорbiditetа.

Klјučnе rеči: hipеrtеnziја, fаrmаkоlоška tеrаpiја, fiksна kоmbinација
epidemiological study, most patients require two or more antihypertensive drugs to adequately control their blood pressure (4). A number of studies have demonstrated the efficiency of a fixed combination (in a single pill) of different classes of antihypertensive agents. These combinations have proven to be safe and efficient because drugs act via different mechanisms, and the side effects of individual drugs were significantly reduced. Additionally, the fixed combination enabled early and effective attainment of target blood pressure levels, a significant increase in treatment compliance and adherence to antihypertensive therapy, a reduction of adverse effects and a reduction of the cardiovascular and cerebrovascular mortality (5). The most commonly used combinations of two anti-hypertensive drugs have been combinations of ACE inhibitors and diuretics and combinations of ACE inhibitors and calcium antagonists. In recent years, research has focused on a triple combination of antihypertensive drugs, with a single tablet encompassing all the above-mentioned advantages of fixed combinations. Several large studies have identified a significant percentage of patients who required three or more antihypertensive drugs to adequately control their blood pressure (ALLHAT-23% of patients; ACCOMPLISH-32% of patients) (6, 7). In terms of efficacy, rationality and safety, a fixed three-in-one combination of an ACE inhibitor, calcium antagonist and diuretic is emerging as an important link in the chain of continued approaches to the current treatment of high blood pressure.

PATIENTS AND METHODOLOGY

Our research is a part of an international, multcentre, randomized prospective study. The objective of the study was to evaluate the clinical efficacy and safety of a fixed-dose combination of Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg in a single pill compared to a fixed combination of Perindopril 5 mg/Indapamide 1.25 with Amlodipine 5 mg given as a separate drug over a period of 12 weeks.

The study included adult patients of both sexes with poorly regulated hypertension who were previously on maximum doses of monotherapy or dual therapy for hypertension (without using Perindopril, Amlodipine and Indapamide in the past two months). The definition of poorly regulated hypertension included systolic blood pressure ≥140 mmHg and <160 mmHg and diastolic blood pressure ≥90 mmHg and <100 mmHg measured at the two different visits. The consumption of grapefruit juice during the study was not allowed due to its interaction with Amlodipine.

Exclusion criteria included the following: minors, pregnant women (positive β-hCG test), breastfeeding women, women of childbearing age with inadequate contraception and the possibility of conception, patients with orthostatic hypotension, obese with a body mass index >32 kg/m², renal impairment, anaemia (haemoglobin <100 g/L), electrolyte imbalance, a history of heart disease (myocardial infarction, heart failure, coronary revascularization, severe aortic or mitral valve stenosis or hypertrophic obstructive myocardialopathy, unstable angina pectoris), heart rhythm disorders, transaminase values that were 1.5 times greater than the reference value (known complicated liver disease: chronic hepatitis, cirrhosis), microalbuminuria >300 mg/24 h, severe gastro-intestinal tract disorders, diabetes mellitus type 1 or 2 under treatment, endocrine diseases (Chushing’s syndrome, acromegalia, hyperparathyroidia), chronic pancreatitis, and history of a severe mental or psychiatric disorder. In addition, patients whose blood pressure was unregulated and exceeded 160/100 mmHg on two measurements with an interval of 15 days were excluded from the study.

Each patient underwent a physical examination at the beginning of the study that included body height and weight measurement, calculated body mass index, 12-lead ECG, heart rate, and screening for microalbuminuria with dipstick strips (if the result was positive, proteinuria in 24-hour urine was required). After 12-hours fasting, blood samples were taken for haematology (haemoglobin, hematocrit, erythrocytes, platelets, leukocytes and leucocyte counts) and biochemical tests (sodium, potassium, chloride, calcium, uric acid, glucose, total protein, triglycerides, cholesterol, ALT, AST, GGT) in the morning.

Patients were divided into two groups. One group received a fixed-dose combination of Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg (‘drug 2’ group), and a second group received two drugs: a combination of Perindopril 5 mg/Indapamide 1.25 mg as one pill and Amlodipine 5 mg given as a separate drug (‘drug 1’ group).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Drug 1</td>
<td>1 Male</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2 Female</td>
<td>2</td>
</tr>
<tr>
<td>Drug 2</td>
<td>1 Male</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2 Female</td>
<td>0</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Drug 1</td>
<td>1 Positive</td>
<td>4</td>
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<tr>
<td></td>
<td>2 Negative</td>
<td>2</td>
</tr>
<tr>
<td>Drug 2</td>
<td>1 Positive</td>
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<td>2 Negative</td>
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<td>HLP</td>
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<td>Drug 1</td>
<td>1 Elevated</td>
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<tr>
<td>Drug 2</td>
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<td></td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Drug 1</td>
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<td></td>
<td>2 Passive</td>
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<td></td>
<td>3 Former</td>
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<td>Drug 2</td>
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Table 1. Demographic characteristics of examined patients and related factors.
Upon enrolment in the study, follow-up visits were performed after 4, 8 and 12 weeks. At every visit, blood pressure was measured both in the sitting and standing position, and heart rate was calculated. Blood pressure was measured using a sphygmomanometer cuff that covered 2/3 arm and included at least 80% of its volume. The measurement was performed three times in both hands with one minute breaks in between measurement; the average value was then calculated.

Before inclusion in the study, all patients provided signed informed consent. The local institution’s Committee of Ethics approved the study. Data were described using descriptive statistical methods and analysed via ANOVA repeated measures. Descriptive statistical methods included measures of central tendency (mean, median), indicators of structure (expressed in percentage) and measures of variability (standard deviation, minimum and maximum value).

RESULTS

The study included 12 patients, each of whom was randomly assigned to one of two groups. The first group included 6 patients (four men and two women) who received “drug 1” (fixed-combination drug Perindopril 5 mg/Indapamide 1.25 mg and Amlodipine 5 mg as a separate drug). The second group also consisted of 6 patients (6 men) who received “drug 2” (triple fixed combination of Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg). The average age of the patients was $40.00 \pm 9.49$ years in the “drug 1” group and $40.67 \pm 10.82$ years in the “drug 2” group. The average body mass index (BMI) for patients on “drug 1” was $29.17 \pm 2.64$ (min 24, max 31), and for patients with “drug 2” the average was $27.67 \pm 3.39$ (min 22, max 32). There was no statistically significant between-group
difference between patients taking “drug 1“ and “drug 2“ in the prevalence of other risk factors for cardiovascular disease (family history, hypercholesterolemia, smoking) (Table 1).

The study showed a significant decline in the average systolic blood pressure (SBP) in both groups from the first to the fifth visit (F = 3.99, p = 0.05).

At the first visit, the average SBP in patients who were taking “drug 1“ was 153 ± 6.57 mmHg; a decrease was noted through the fifth visit at which time the average SBP was 132.5 ± 25.38 mmHg. In patients who taking “drug 2“ the average SBP (measured at the first visit) was 149.17 ± 24.06 mmHg. This value significantly decreased to SBP 140.5 ± 8.02 mmHg by the fifth visit (Figure 1). The results also showed a significant reduction in mean diastolic blood pressure (DBP) from the first to fifth visit (F = 20.16, p <0.05). At the first visit, the average DBP for patients who taking “drug 1 “ was 94.83 ± 3.22 mmHg. After a slight increase noted at visit two, a decrease in DBP was recorded through the fifth, visit, at which time the average DBP was 84.50 ± 10.29 mmHg. The average value of DBP for patients taking “drug 2“ was 94.00 ± 3.22 mmHg at the first visit. This average DBP value significantly decreased to 83.83 ± 5.98 mmHg by the fifth visit (Figure 2). Our results showed no statistically significant difference between “drug 1“ and “drug 2“ in their effects on the average values of the SBP (F = 0.24, p> 0.05) and DBP (F = 1.29, p> 0.05) between the first and fifth visit.

In our study, a higher percentage of patients achieved target blood pressure (<140/90 mmHg) in the group with triple fixed dose combination drugs (69.7%) compared to patients taking a combination of three drugs in two tablets (50%). There was no statistically significant difference between patients in the “drug 1“ and “drug 2“ groups in terms of average heart rate frequency between visit 1 and visit 5. No adverse effects from the drug therapy or any signs and symptoms of other diseases were reported during the study period in all patients.

DISCUSSION

Our study showed that the use of a fixed combination in one pill (Perindopril 5 mg/Indapamide 1.25 mg/Amlodipine 5 mg) as well as a combination of two pills (fixed combination of Perindopril 5 mg/Indapamide 1.25 and Amlodipine 5 mg) during the 12 weeks of therapy produced significant decreases in both systolic and diastolic blood pressure in patients with unregulated essential hypertension without comorbidity. The fixed combination of three drugs at the end of the monitoring period had lower DBP and slightly higher SBP compared to patients who used two drugs, although this difference was not statistically significant.

The effective treatment of hypertension is based on the regular use of medication. Numerous studies have shown that the attainment of the target blood pressure (<140/90 mmHg) requires the use two or more drugs (8, 9) According to the JNC 7 report (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure), polypharmacy is marked as one of the major obstacles in achieving target blood pressure values due to poor compliance with the medication regimen (10). Therefore, the report recommended a fixed combination of drugs. The first use of triple-fixed drug combinations was described in 1966. It introduced the use of a combination of reserpine, hydralazine, and hydrochlorothiazide, which was quickly abandoned due to the drugs’ adverse effects (11). Since the 1980s, several fixed drug combinations have been introduced. The European and American Guidelines (2003) for the treatment of hypertension recommended an initial treatment of hypertension with fixed-combination drugs (12). These recommendations were based on a number of studies which have shown that the use of fixed combinations is associated with better compliance, fewer side effects and faster achievement of target blood pressure values (13). A meta-analysis that included 11,925 respondents from nine studies, of which three were subjects with hypertension, came to the conclusion that the use of fixed combinations of drugs reduced noncompliance by 24-26% (14).

Today, triple fixed-dose combinations consist of different drug groups. Calcium antagonists and diuretics are the most common, combined with an ACE inhibitor, receptor antagonist ATII or aliskiren as a third drug. Calhoun and colleagues showed that the fixed combination of Aliskiren/Valsartan/Hydrochlorothiazide (HTZ) showed greater reduction in blood pressure and a higher percentage of patients successfully reaching the target blood pressure compared to a control group that received a fixed combination of Aliskiren/Valsartan and Val-sartan/HTZ (15). Opari and colleagues in the TRINITY study yielded similar results, in which the use of a fixed combination of Olmesartan/Amlodipine/HTZ was superior in terms of ef-ficacy and tolerability compared to the control group with a dual-fixed combination of these drugs (16).

The combination of Perindopril/Indapamide/Amlodipine has a special therapeutic significance as one of the possible fixed combinations of antihypertensive drugs. In this combination, drugs act by different mechanisms in lowering blood pressure, and Perindopril and Amlodipine have been shown to have strong antiatherosclerotic effects. The calcium antagonist Amlodipine has a renin-independent mechanism of lowering blood pressure by blocking the L-calcium channels in the cell-smooth muscle arteriolar, which causes its vasodilatation. The diuretic Indapamide affects natriuresis, peripheral vascular resistance, and indirect stimulation of the renin activity. The ACE inhibitor Perindopril inhibits the system RAAS (renin-angioten-sin-aldosterone system). The combination of the renin-dependent and renin-independent mechanisms leading establishing a balance between renin and sodium, reduced blood pressure and reduced adverse effects of individual components of the drug. Several studies have demonstrated a significant antihypertensive and antiatherosclerotic effect of the combination of these drugs. The ASCOT
study showed a strong effect of the combination of Perindopril/Amlodipine in reducing not only blood pressure but also cardiovascular and cerebrovascular target events (17). The EFFICIENT study has shown great efficacy and tolerability of a fixed combination of Amlodipine/Indapamide in patients with uncontrolled primary hypertension (18).

The effect of the triple combination of these drugs has been confirmed by the results of the PIANIST study (19). The study included 4,731 patients with high or very high cardiovascular risk with hypertension that was not well controlled despite antihypertensive therapy. Patients were followed for 4 months. After switching to a fixed combination of Perindopril/Indapamide/Amlodipine, a decrease was observed in the mean arterial pressure of 28.3/13.8 mmHg and blood pressure was regulated at 72%, which is similar to the results of our research. Despite the fact that patients did not have regulated blood pressure first, significant results were observed after only a month of switching to a fixed combination of drugs. Additionally, this study recorded a significant decrease of blood pressure variability.

Finally, it should be noted that it is shown that fixed triple drug combinations additionally enhance compliance and adherence to therapy and have a significant positive effect on the cost of antihypertensive therapy (20).

CONCLUSIONS

This study demonstrated significant efficiency and safety of a fixed combination of three drugs (Perindopril, Indapamide and Amlodipine) in one tablet in patients with uncontrolled essential hypertension without associated comorbidity. The application of this drug is characterized by a rapid achievement of target blood pressure, excellent adherence to the compliance and the absence of side effects. A limitation of this study was its relatively small number of subjects and the short follow-up period.

Acknowledgments

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Conflict Of Interest

The authors declare that they have no conflicts of interest.

REFERENCES


