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Original Moxonidine and Generics: Where is the Edge of Difference?

Aim	To compare the efficacy of adding original moxonidine and its generics to previous ineffective antihypertensive therapy in patients with poorly controlled arterial hypertension (AH).
Material and methods	This observational prospective non-randomized study included 120 patients with poorly controlled blood pressure on the previous antihypertensive therapy. All patients underwent clinical evaluation, including anthropometric and laboratory indexes, and 24-hour blood pressure monitoring (24-h BPM) at baseline and after 12 weeks of observation. Office systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were recorded after 4 and 12 weeks of treatment. During the observation period, 4 equal groups were formed: group 1, Physiotens was added to the treatment; group 2, Moxonitex; group 3, Moxonidine SZ; and group 4, Moxonidine Canon. Statistical analysis was performed with the StatTech v.4.2.7 software (© StatTech, Russia).
Results	After 4 weeks of therapy, the BP target was achieved significantly more frequently in group 1 (63% of patients) compared to groups 2 (36.7% of patients), 3 (16.7% of patients), and 4 (16.7% of patients) ($p<0.05$). At 12 weeks, office SBP, DBP, and HR were significantly decreased in all groups, but the decrease was significantly greater in group 1. The therapy was associated with a more pronounced decrease in all studied 24-h BPM parameters in the Physiotens group than in other groups, as well as with a significantly more frequent normalization of the 24-h BP profile, in 66.7% of patients vs. 46.7%, 33.4%, and 23.2% of patients in groups 2, 3, and 4, respectively.
Conclusion	The treatment with original moxonidine demonstrated advantages over generic drugs in terms of achieving the BP goal, reducing office BP and HR, and improving 24-h BPM parameters.

Keywords	Original moxonidine; physiotens; generics; uncontrolled arterial hypertension
For citations	Skibitsky V. V., Fendrikova A. V., Skibitsky A. V., Sirotenko D. V., Timofeeva O. V. Original Moxonidine and Generics: Where is the Edge of Difference? Kardiologiia. 2024;64(8):24–31. [Russian: Скибицкий В. В., Фендрикова А. В., Скибицкий А. В., Сиротенко Д. В., Тимофеева О. В. Оригинальный моксонидин и генерики: где проходит грань отличий? Кардиология. 2024;64(8):24–31].

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The comparability of the effects of original and generic drugs is a topic frequently addressed by medical professionals. The extensive use of generic pharmaceuticals in clinical practice has facilitated the accumulation of disparate experiences pertaining to their efficacy, ranging from skepticism regarding the comparable efficacy of generic drugs to confidence in their full therapeutic equivalence to original drug. The results of a comprehensive systematic review of 186 papers examining the attitudes of medical professionals, pharmacists, and patients towards the use of generic drugs are inconclusive. In the United States and Italy, physicians tend to prefer prescribing branded drugs, whereas in other countries, including the Czech Republic, Nigeria, Greece, and Ireland, they physicians tend to prefer prescribing generic medications [1]. It is evident that the administration of generic drugs to a certain extent solves the problem of the accessibility of modern pharmacotherapy to a diverse patient population. However, the decision between original and generic drugs should be an informed one, based on the findings of bioequivalence assessments and independent comparative clinical trials.

Generic drugs are frequently administered in the treatment of cardiovascular disorders, particularly hypertension. Nevertheless, the therapeutic equivalence of antihypertensive branded drugs and generics is not always subjected to evaluation. Nevertheless, this data may prove beneficial when selecting a particular medication.

Moxonidine is among the most frequently prescribed medications for the treatment of hypertension. A review of the Russian State Register of Medicines (https://grls.rosminzdrav.ru/) reveals that 22 generic versions of moxonidine have been registered in the Russian Federation to date. To date, only a limited number of national clinical trials have been conducted in Russia with the objective of comparing the efficacy of generic and original moxonidine (Physiotens®). In their study, V. V. Ruksin et al. [2] investigated the efficacy of Physiotens® and two generic medications in reducing blood pressure (BP) in patients with elevated BP who did not have life-threatening conditions. Moreover, data on the comparative in vitro dissolution kinetics of the original and generic moxonidine preparations have been published [3]. Nevertheless, no clinical studies have been conducted to evaluate the efficacy of

ISSN 0022-9040. Kardiologiia. 2024;64(8). DOI: 10.18087/cardio.2024.8.n2731

Central illustration. Original Moxonidine and Generics: Where is the Edge of Difference?

Real- world clinical practice study
Comparison of the efficacy of the original and generic moxonidine in patients with uncontrolled hypertension

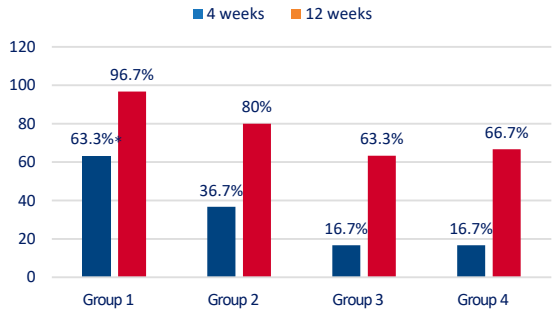
- 55 men/65 women
- Median age, years – 60 [51.8; 66.0]
- Median office SBP, mm Hg – 155.0 [150.0; 160.0]
- Median office DBP, mm Hg – 93.5 [90.0; 95.0]

Groups (30 patients in each):
- Group 1 -+ original moxonidine
- Group 2 -+ generic moxonidine 1
- Group 3 -+ generic moxonidine 2
- Group 4 -+ generic moxonidine 3

Follow-up period – 12 months

Endpoints:
- Achievement of the target office BP
- 24-h BP monitoring

Achievement of the target office BP in 4 and 12 weeks (% of patients)



* p < 0.05 statistical significance for the differences in achieving target BP levels at Visit 2 in Group 1 compared to Groups 3 and 4.

Comparison of changes in 24-hour BP monitoring indicators

- SBPd: original is superior to generic counterparts 1, 2, and 3 (p < 0.05)
- DBPd: original is superior to generic counterparts 1, 2, and 3 (p < 0.05)
- SBPd load: original is superior to generic counterparts 1, 2, and 3 (p < 0.05)
- DBPd load: original is superior to generic counterparts 1, 2, and 3 (p < 0.05)
- DBPn load: original is superior to generic counterparts 1, 2, and 3 (p < 0.05)
- DBPn MS: original is superior to generic counterparts 1, 2, and 3 (p < 0.05)

SBPd, daytime systolic blood pressure; DBPd, daytime diastolic blood pressure; MS, morning surge.

Physiotens® and its generic counterparts during regular use over several months in patients with hypertension, which prompted the initiation of this analysis.

Objective

The objective of this study was to compare the efficacy of adding original moxonidine and its generic counterparts to prior ineffective antihypertensive therapy in patients with uncontrolled hypertension.

Material and Methods

The study was designed as an observational, prospective, comparative, and parallel study, and was conducted in three clinical outpatient centers in Krasnodar. It was conducted with the participation of cardiologists and therapists. A total of 120 patients, aged between 37 and 75 years old, with uncontrolled hypertension despite previous antihypertensive therapy, were included in the study. The decision to include a patient in the program was made by a physician, guided by the intention to intensify antihypertensive therapy in order to ensure the achievement of the target BP level. All patients provided informed consent to participate in the study. Individuals with documented resistant hypertension, symptomatic hypertension, coronary heart disease, chronic heart failure NYHA class III–IV, complex rhythm and conduction disorders, intolerance, or contraindications to moxonidine administration were excluded.

Following the physician's decision that the patient was eligible for inclusion in the program, the original moxonidine or one of the three available generic counterparts was incorporated into the existing treatment regimen at a daily dose of 0.2–0.4 mg, contingent upon the patient's baseline BP level. The attending physician was responsible for selecting moxonidine for a specific patient and communicating this decision to the coordinating investigator. It was the responsibility of the coordinating investigator to monitor patient enrollment and halt it once the requisite number of respondents had been included in the groups. Four groups were established: Group 1 (n = 30) received the original moxonidine Physiotens® (Abbott Laboratories/Veropharm), Group 2 (n = 30) received the generic moxonidine Moxonitex (Sandoz), Group 3 (n = 30) received the generic drug Moxonidine-SZ (Severnaya Zvezda), and Group 4 (n = 30) received the generic drug Moxonidine Kanon (Kanonpharma Production).

At the time of enrollment in the program (Visit 1), a comprehensive physical examination was conducted, including the determination of anthropometric parameters (waist circumference, height, weight, body mass index (BMI)), threefold measurements of BP and heart rate (HR). Laboratory tests were conducted to assess serum glucose levels, lipid profile parameters, creatinine (with subsequent calculation of the glomerular filtration rate using the CKD-EPI formula), and glycated hemoglobin (HbA1C).

During the same visit, the 24-hour BP monitoring was performed using the BPLabVasotens system (OOO Petr Telegin, Russia). The mean values of daytime and nighttime systolic and diastolic blood pressure (SBP and DBP), SBP and DBP load, SBP and DBP variability (Var), as well as SBP and DBP morning surge (MS) and morning surge rate (MSR) were analyzed. In accordance with the findings of 24-hour BP monitoring, distinct daily BP profiles were identified: dipper,non-dipper, over-dipper, and night-peaker.

Following a four-week period (± 3 days), patients were invited to attend a medical visit for the purposes of ascertaining trends in BP and HR, as well as identifying any adverse events associated with the therapy (Visit 2). In the event that the patient's office BP did not meet the target values outlined in the current clinical guidelines [4], the dose of moxonidine was increased to 0.4–0.6 mg/day.

Over the subsequent eight-week period, the efficacy of the treatment was assessed through telephone contact. In the event that an adjustment in dosage was deemed necessary, the investigators were authorized to elevate the moxonidine dose to 0.6 mg/day.

The final visit (Visit 3) was scheduled to occur 12 weeks (± 3 days) after the initiation of moxonidine therapy. During this visit, a comprehensive clinical examination was conducted, including an assessment of blood pressure (BP), heart rate (HR), and repeated determination of anthropometric parameters. Additionally, laboratory tests and 24-hour BP monitoring were performed, as well as an assessment of possible adverse events.

The statistical analysis was conducted using the software program StatTech v.4.2.7 (OOO StatTech, Russia). Given that the number of subjects in each group was fewer than 50, the quantitative indicators were evaluated for conformity to a normal distribution using the Shapiro-Wilk test. Normally distributed quantitative indicators were described using the mean (M) and standard deviation (SD). Non-normally distributed quantitative data were described using the median (Me) and the lower and upper quartiles (Q1 – Q3).

Categorical data were expressed as absolute values and percentages. Comparison of groups on a normally distributed quantitative indicator was performed using univariate analysis of variance, and post hoc comparisons were performed using Tukey's test (assuming equal variance) and Games-Howell test (assuming unequal variance).

Groups were compared by non-normally distributed quantitative indicators using the Kruskal-Wallis test, and post hoc comparisons were performed using Dunn's test with Holm's correction.

Pearson's chi-squared test was used to compare percentages in the analysis of multifactor contingency tables.

When comparing three or more dependent samples of non-normally distributed data, the nonparametric Friedman test was used with post hoc comparisons using the Conover-Iman test with Holm's correction. The observed differences were deemed statistically significant at the $p < 0.05$ level.

Results

Patient characteristics

With regard to the baseline anamnestic, clinical, and laboratory parameters, no statistically significant differences were observed between the four study groups, with the exception of age (Table 1).

In all groups, the majority of patients were found to be overweight or obese, with varying degrees of severity (Table 2). No statistically significant differences were observed in the number of patients with varying degrees of obesity across the groups.

Moreover, blood sugar and HbA1C tests enabled the diagnosis of prediabetes in 8 (26.7%), 10 (33.3%), 12 (40%), and 6 (20%) patients in Groups 1, 2, 3, and 4, respectively.

In accordance with the established protocol, patients with a history of ineffective therapeutic interventions were included in the study. At the time of inclusion, the majority of patients were receiving a combination of two drugs: a renin-angiotensin system inhibitor and a diuretic (n = 78, 65%) or a renin-angiotensin system inhibitor and a calcium channel blocker (n = 20, 16.7%); 8 patients (6.6%) were taking a combination of three antihypertensive agents. Different pharmacotherapy options were presented at comparable rate across all study groups.

Achievement of the target BP level

The achievement of target BP values in the context of supplementary moxonidine administration was evaluated at weeks 4 and 12 The integration of moxonidine into an antihypertensive regimen led to a statistically significant increase in the frequency of target BP registration at the fourth week of observation when compared to two generic medications: Moxonidine SZ and Moxonidine Canon. By week 12, the aforementioned trend persisted, yet the differences between the groups were no longer statistically significant (Figure 1).

Changes in office BP and HR values during therapy

A statistically significant reduction in office values of SBP, DBP, and HR was observed in all groups (Table 3). A post hoc analysis revealed that the magnitude of the office SBP reduction in Groups 1 and 2 was statistically significantly greater than that observed in Groups 3 and 4. The patients who received Physiotens as part of their antihypertensive therapy exhibited a significantly more pronounced reduction in both office SBP and HR compared to the patients in the other three groups (see Table 3). A statistically significant superiority in terms of effect on SBP, DBP, and HR was observed in patients taking Physiotens compared to those taking generic drugs, as early as the second visit.

ISSN 0022-9040. Kardiologiia. 2024;64(8). DOI: 10.18087/cardio.2024.8.n2731

Table 1. Anamnestic, clinical, and laboratory parameters at the time of inclusion in the study (Me [Q1-Q3] and M ± SD)

Parameter	Group 1, n = 30	Group 2, n = 30	Group 3, n = 30	Group 4, n = 30
Age, years	63.0 [58.3–67.8]	55.5 [48.5–60.0]*	64.0 [58.0–67.0]**	56.5 [49.3–62.8]***
Duration of hypertension, years	12.0 ± 6.2	11.5 ± 5.3	13.3 ± 5.9	15.8 ± 3.8
Male, n (%)	12 (40)	15 (50)	11 (36.7)	17 (56.7)
Office SBP, mm Hg	155.5 [150.0–161.5]	155.0 [150.0–160.0]	152.5 [150.0–160.0]	155.0 [150.0–165.0]
Office DBP, mm Hg	90.0 [90.0–97.3]	95.0 [90.0–95.0]	90.0 [85.0–95.0]	95.0 [90.0–100.0]
Office HR, bpm	76.0 [67.8–81.0]	71.5 [68.3–78.0]	73.0 [67.8–77.8]	71.5 [65.3–78.5]
BMI, kg/m2	31.6 [29.6–35.5]	31.3 [28.8–34.9]	30.6 [29.5–35.6]	30.2 [27.9–31.9]
Blood serum sugar, mmol/L	5.7 [5.5–6.0]	5.6 [5.4–5.9]	5.8 [5.3–6.0]	5.6 [5.4–5.8]
HbA1c, %	5.69 ± 0.5	5.8 ± 0.5	5.9 ± 0.3	5.5 ± 0.3

* $p < 0.05$ statistical significance of the differences of the indicator between Groups 2 and 1; ** $p < 0.05$ statistical significance of the differences of the indicator between Groups 3 and 2; *** $p < 0.05$ statistical significance of the differences of the indicator between Groups 4 and 3. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; HbA1C, glycated hemoglobin.

Table 2. Distribution of patients in groups based on BMI categories, n (%)

Patient categories based on BMI	Group 1, n = 30	Group 2, n = 30	Group 3, n = 30	Group 4, n = 30
Normal weight	0 (0.0)	2 (6.7)	1 (3.3)	2 (6.7)
Overweight	10 (33.3)	9 (30.0)	7 (23.3)	9 (30.0)
Obesity grade 1	11 (36.7)	13 (43.3)	13 (43.3)	17 (56.7)
Obesity grade 2	6 (20.0)	6 (20.0)	6 (20.0)	2 (6.7)
Obesity grade 3	3 (10.0)	0 (0.0)	3 (10.0)	0 (0.0)

BMI, body mass index.

Table 3. Changes in office values of SBP, DBP, and HR in the groups following 4 and 12 weeks of pharmacotherapy (Me [Q1–Q3])

	Group 1, n = 30	Group 2, n = 30	Group 3, n = 30	Group 4, n = 30
	Changes in office SBP, mm Hg			
Visit 1	155.5 [150.0–161.5]	155.0 [150.0–160.0]	152.5 [150.0–160.0]	155.0 [150.0–165.0]
Visit 2	127.0 [125.0–137.3]*	134.5 [129.3–139.5]*	137.0 [132.0–144.3]*	140.0 [136.0–147.3.0]*
Visit 3	124.5 [120.0–130.0]**	126.5 [125.0–130.0]**	127.7 [127.3–136.0]**	128.0 [126.0–134.8]**
Visit 2: p group 2 – group 4 = 0.027; p group 3 – group 1 < 0.001; p group 4 – group 1 < 0.001. Visit 3: p group 3 – group 1 = 0.027; p group 4 – group 1 = 0.039.				
	Changes in office DBP, mm Hg			
Visit 1	90.0 [90.0–97.3]	95.0 [90.0–95.0]	90.0 [85.0–95.0]	95.0 [90.0–100.0]
Visit 2	77.5 [75.0–80.0]*	82.0 [80.0–85.0]*	80.0 [80.0–90.0]*	84.5 [80.0–90.0]*
Visit 3	73.0 [70.0–77.0]**	76.5 [74.0–80.0]**	76.0 [73.5–85.8]**	75.5 [73.3–80.0]**
Visit 2: p group 2 – group 1 = 0.001; p group 3 – group 1 < 0.001; p group 4 – group 1 < 0.001. Visit 3: p group 2,3,4 – group 1 = 0.024				
	Changes in office HR, bpm			
Visit 1	76.0 [67.8–81.0]	71.5 [68.3–78.0]	73.0 [67.8–77.8]	71.5 [65.3–78.5]
Visit 2	67.5 [64.0–73.0]*	72.0 [68.5–75.8]*	72.0 [70.0–77.8]*	70.0 [68.0–74.8]
Visit 3	65.0 [60.3–69.5]**	70.0 [66.3–73.0]**	70.0 [68.3–75.0]**	70.0 [66.0–72.0]
Visit 2: p group 3 – group 1 = 0.026 Visit 3: p group 2,3,4 – group 1 < 0.05				

* $p < 0.05$ statistical significance of the differences in the indicator at visits 1 and 2;
** $p < 0.05$ statistical significance of the differences in the indicator at visits 2 and 3.
SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

It is noteworthy that in Group 1, the initial dose of Physiotens (0.2 mg/day) was sufficient to achieve the aforementioned outcomes in 40% of cases (n = 12). In contrast, in Groups 2, 3, and 4, such this dose was administered in only 5 (16.7%), 2 (6.7%), and 4 (13.3%) patients, respectively ($p < 0.05$). In the remaining patients, the dosage of the medication was increased to 0.4 mg/day at Visit 2.

Subsequently, it was necessary to increase the dosage to the maximum level (0.6 mg/day) on average in 15–20% of patients in each group.

Changes in 24-hour BP monitoring indicators during therapy

Following a 12-week period, positive alterations in the indicators of 24-hour BP monitoring were also documented in the study groups (Table 4). Nevertheless, only the groups of patients who received Physiotens and Moxonitex as part of their antihypertensive therapy demonstrated statistically significant alterations in all parameters. The intergroup post hoc analysis revealed a statistically significant decrease in daytime and nighttime SBP and DBP, daytime SBP and DBP load, nighttime SBP load, as well as SBP MS in Group 1 as compared to all other groups (see Table 4).

The enhancement of mean values for 24-hour BP monitoring indicators was accompanied by the optimization of the 24-hour BP profile in a subset of patients. However, a statistically significant increase in the number of patients exhibiting a 24-hour dipper BP curve was observed exclusively in Groups 1 and 2 (Table 5).

Changes in BMI during therapy

The impact of the therapeutic intervention on BMI was assessed during the study (Table 6). A statistically significant and comparable decrease in BMI was observed in all groups of respondents after a 12-month period (Table 6).

Table 4. Results of 24-hour BP monitoring in the study groups at the baseline and after 12 weeks of therapy (Me [Q1-Q3] and M ± SD)

Parameter	Group 1		Group 2		Group 3		Group 4		p
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	
SBPd. mm Hg	151.8 [143.0–156.1]	129.0 [125.3–131.0]*	146.0 [143.0–152.8]	133.0 [130.0–135.0]*	143.5 [142.0–149.5]	135.0 [132.0–136.8]*	145.0 [141.3–155.8]	134.0 [132.3–135.8]*	p_{2-1} = 0.003 p_{3-1} <0.001 p_{4-1} <0.001
DBPd. mm Hg	84.6±10.6	72.3±5.6*	86.9±9.8	78.9±6.1*	82.4±8.5	77.8±7.2*	87.7±9.7	80.3±7.2*	p_{2-1} < 0.001 p_{3-1} = 0.008 p_{4-1} <0.001
SBPd load. %	76.5 [41.8–91.8]	18.5 [9.3–26.8]*	73.5 [39.8–89.3]	37.0 [15.8–49.0]*	61.5 [25.0–77.0]	29.0 [19.0–52.0]*	52.0 [25.0–77.0]	28.5 [15.0–51.5]**	p_{2-1} = 0.037 p_{3-1} = 0.018 p_{4-1} = 0.037
DBPd load. %	42.0 [25.0–57.8]	15.0 [8.0–21.8]*	63.0 [36.3–76.3]	34.5 [26.0–45.8]*	41.0 [20.3–64.3]	30.0 [17.0–41.5]*	57.9 [26.3–82.8]	36.5 [14.8–58.5]**	p_{2-1} = 0.037 p_{3-1} = 0.018 p_{4-1} = 0.037
SBPd var. mm Hg	15.5 [13.0–19.5]	10.6 [8.0–12.0]*	16.0 [12.3–18.0]	11.0 [10.0–12.8] *	16.0 [14.0–19.0]	14.0 [12.3–15.8] *	13.0 [11.2–17.0]	11.5 [10.0–14.8]*	p_{2-3} = 0.01 p_{3-1} <0.001
DBPd var. mm Hg	11.4 [8.2–13.0]	9.0 [8.0–10.0]**	10.0 [8.0–10.8]	8.0 [7.0–9.0]*	10.5 [9.0–11.8]	9.0 [8.0–10.0]**	9.0 [7.3–10.8]	9.0 [8.0–10.5]	0.094
SBPn. mm Hg	137.0 [127.0–143.9]	114.0 [110.3–117.0]*	138.0 [135.0–143.5]	119.5 [116.0–121.0]*	136.0 [129.0–144.8]	120.0 [115.3–125.0]*	133.5 [125.8–140.0]	117.0 [112.1–125.0]*	p_{2-1} = 0.008 p_{3-1} = 0.001
DBPn. mm Hg	76.5 [72.0–82.2]	67.5 [63.3–70.4]*	77.5 [71.5–84.0]	70.0 [67.3–74.8]*	75.0 [66.0–79.0]	68.5 [65.0–73.8] *	77.0 [74.0–83.0]	73.5 [70.0–77.8]**	p_{4-1} = 0.004
SBPn load. %	82.5 [50.8–98.5]	25.0 [5.3–46.6]*	83.0 [45.8–100.0]	35.0 [24.0–44.5]*	83.5 [52.5–98.0]	44.5 [22.5–63.3]*	65.5 [40.5–92.1]	32.0 [18.3–54.8]*	0.093
DBPn load. %	72.0 [42.3–85.0]	24.5 [15.3–34.0]*	85.0 [43.8–100.0]	46.5 [29.3–63.3]*	74.5 [30.8–89.0]	48.0 [33.5–62.8]*	81.0 [41.3–96.3]	44.5 [34.7–67.0]**	p_{2-1} = 0.003 p_{3-1} = 0.003 p_{4-1} <0.001
SBPn var. mm Hg	13.1 [11.0–15.8]	8.3 [6.8–9.8]*	11.0 [10.0–14.8]	9.0 [7.0–11.0]*	12.0 [11.0–14.8]	10.0 [10.0–12.0]**	12.1 [9.0–15.0]	10.5 [9.1–12.0]	p_{3-1} = 0.005 p_{4-1} = 0.003
DBPn var. mm Hg	9.2 [7.0–12.0]	7.8 [5.3–9.0]**	9.0 [7.0–12.0]	7.0 [6.0–9.0]**	9.1 [7.3–10.0]	8.0 [6.3–10.8]	8.5 [7.0–10.8]	8.7 [7.1–10.7]	0.146
SBP MS. mm Hg	50.1±15.7	31.2±10.5*	46.7±18.1	39.6±12.5**	48.5±10.9	42.9±10.2*	42.8±19.4	39.4±12.2	p_{2-1} = 0.03 p_{3-1} <0.001 p_{4-1} = 0.025
DBP MS. mm Hg	38.5 [28.0–47.3]	25.0 [20.0–31.0]*	31.5 [22.3–38.8]	25.0 [20.5–30.8]**	34 [28.0–38.0]	27.0 [22.3–37.0]**	30.5 [22.3–37.8]	31.0 [24.3–40.0]	0.087
SBP MSR. mm Hg/h	21.5 [15.3–35.5]	14.5 [8.5–21.8]*	20.5 [11.5–42.3]	19.0 [10.0–23.8]*	15.5 [11.3–29.0]	15.0 [11.3–20.3]	16.5 [13.0–24.3]	15.0 [12.0–17.8]**	0.555
DBP MSR. mm Hg/h	14.5 [9.6–27.5]	9.0 [6.0–15.0]*	11.5 [8.5–14.0]	8.5 [5.3–12.8]**	13.5 [7.5–18.8]	11.0 [10.0–15.0]	10.0 [7.0–19.3]	10.0 [6.3–16.0]	0.292

* p < 0.001 statistical significance of the differences between the indicators at the baseline and after 12 weeks of therapy;
** p < 0.05 statistical significance of the differences between the baseline and after 12 weeks of therapy.

ISSN 0022-9040. Kardiologiia. 2024;64(8). DOI: 10.18087/cardio.2024.8.n2731

Discussion

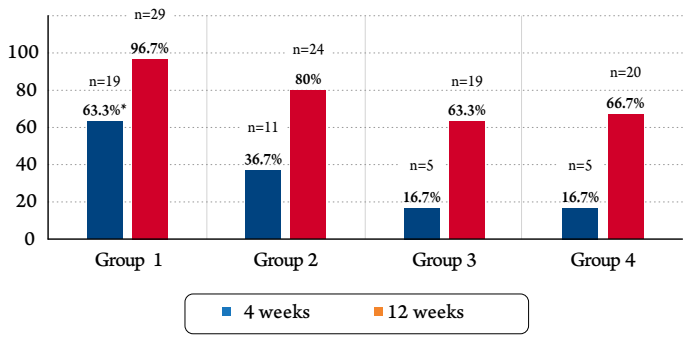
The present study sought to compare the efficacy of adding original moxonidine (Physiotens) and three generic drugs (Moxonitex, Moxonidine CZ, Moxonidine Canon) to previous antihypertensive therapy in subjects with hypertension who had not reached target BP values. At the time of enrollment, patients in the four groups did not differ in key clinical and laboratory parameters except for age. It should be noted that the vast majority of patients enrolled in the study were overweight or obese to varying degrees, and 36 of 120 patients (30%) were diagnosed with prediabetes.

The incorporation of Physiotens into the therapeutic regimen resulted in a more rapid achievement of target BP levels in comparison to the administration of the generic pharmaceuticals, accompanied by a statistically significant diminution in the necessity for an escalation in the dosage of the original drug. Notwithstanding a notable decline in office BP and HR values across all groups, a more pronounced reduction in SBP was observed at Visit 3 in the Physiotens and Moxonitex groups. Additionally, positive changes in DBP and HR were statistically more significant in Group 1 compared to the other groups.

Our findings demonstrate partial correlation with the study conducted by V.I. Podzolkov et al., wherein the incorporation of Physiotens into the combination of an angiotensin-converting enzyme inhibitor and a diuretic resulted in the attainment of the target BP level after 24 weeks in 90% of patients with hypertension and metabolic syndrome [5]. Furthermore, the study revealed statistically significant changes in both nighttime and daytime SBP and DBP as early as Week 12, a finding that was also demonstrated in our own research. Similar findings were reported by S.V. Nedogoda et al. In a study where an unfixed combination of perindopril 10 mg/day and moxonidine 0.4 mg/day was administered, target BP values were achieved in 64.7% of patients with hypertension and metabolic syndrome [6]. Furthermore, as evidenced in the literature, the incorporation of moxonidine into a combination therapeutic regimen for patients with hypertension and early carbohydrate metabolism disorders was associated with a statistically significant improvement in 24-hour BP monitoring parameters [7].

It was anticipated that the introduction of moxonidine into the therapeutic regimen would result in a reduction in HR. Similar results were observed in the MARRIAGE study, in which the administration of moxonidine in patients with hypertension and carbohydrate metabolism disorders resulted in both the normalization of BP and a mean reduction in HR of 3.5 bpm (p = 0.017) [8]. The observed changes in HR cannot be attributed solely to the sympatholytic effect of moxonidine. In animal experiments, the administration of moxonidine was observed to result in the activation of the parasympathetic

Figure 1. Frequency of achieving target BP in the treatment groups after 4 weeks (Visit 2) and 12 weeks (Visit 3)



* p < 0.05 statistical significance of the differences in achieving target BP levels at Visit 2 in Group 1 compared to Groups 3 and 4.

Table 5. Number of patients with different 24-hour BP profiles in the study groups at the baseline and after 12 weeks of therapy (n (%))

BP profile	Group 1, n = 30		Group 2, n = 30		Group 3, n = 30		Group 4, n = 30	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
dipper	4/13.3	20*/66.7	6/20	14*/46.7	7/23.3	10/33.4	4/13.3	7/23.2
non-dipper	19/63.4	9*/30	21/70.0	13/43.3	16/53.3	15/50	18/60.1	18/60.1
over-dipper	2/6.6	–	1/3.3	1/3.3	4/13.3	2/6.6	4/13.3	2/6.6
night-peaker	5/16.7	1*/3.3	2/6.6	2/6.6	3/10.1	3/10	4/13.3	3/10.1

* p < 0.05 statistical significance of the differences in the number of patients at Visits 1 and 3.

Table 6. Changes in BMI in the study groups at the baseline and after 12 weeks of therapy (Me [Q1-Q3])

Parameter	Group 1, n = 30	Group 2, n = 30	Group 3, n = 30	Group 4, n = 30
	BMI, kg/m2			
Visit 1	31.6 [29.6–35.5]	31.3 [28.8–34.9]	30.6 [29.6–35.6]	30.2 [27.9–31.9]
Visit 3	31.4 [29.4–35.4]*	31.0 [28.4–33.6]*	30.4 [29.9–34.8]*	29.9 [27.8–31.3]*

p = 0.207 (statistical significance of the differences in BMI between the groups at Visit 3)

* p < 0.05 statistical significance of the differences in the indicator at Visits 1 and 3. BMI, body mass index.

nervous system due to the stimulation of central alpha-2 adrenoreceptors [9]. A single administration of moxonidine to healthy volunteers resulted in an increase in cardiovagal effects and a decrease in myocardial sympathetic activity [10].

One of the primary mechanisms by which moxonidine is indicated for individuals with hypertension, obesity, and carbohydrate metabolism disorders is through the correction of insulin resistance, which is closely associated with hypersympathicotonia. The ALMAZ study demonstrated an increase in insulin sensitivity and a reduction in the area under the curve (AUC) for insulin in the group of subjects with hypertension and carbohydrate metabolism disorders who were treated with moxonidine [11]. The most notable alterations in these parameters were observed in patients exhibiting HR exceeding 80 bpm. In the study conducted by A.F. Sanjuliani et al., monotherapy with moxonidine resulted in a notable reduction in plasma levels of adrenaline and noradrenaline, as well as insulin and leptin, in patients with hypertension and obesity [12]. It is notable that in individuals with obesity, an increase in blood leptin levels is correlated with the activity of the sympathetic nervous system [13]. Consequently, the correction of hyperleptinemia represents an additional mechanism underlying both the antihypertensive and heart rate-lowering effects of moxonidine.

As previously stated, moxonidine treatment has been linked to favorable metabolic outcomes, which was indirectly demonstrated in our study. A statistically significant reduction in BMI was observed across all patient groups. The reduction of body weight in individuals with metabolic disorders during moxonidine administration has been demonstrated in multiple studies. For example, in the ALMAZ study, moxonidine therapy resulted in a reduction in BMI and blood sugar levels that was nearly equivalent to that achieved with metformin [11]. Similar outcomes were observed in the MERSY study, in which a reduction in body weight was documented in subjects with uncontrolled hypertension and metabolic syndrome following six months of treatment with moxonidine [14], as well as in the COMPASS study, in which the efficacy of moxonidine therapy was investigated in postmenopausal women with hypertension [15].

The results of our study demonstrated a significant antihypertensive effect in all groups. Nevertheless, the demonstrated superiority of the original moxonidine Physiotens over generic drugs in terms of achieving target BP values, BP reduction, and positive changes in 24-hour BP monitoring parameters is a noteworthy finding. It is notable that the findings of the aforementioned studies (ALMAZ, MERSY, etc.) were derived from the use of the original moxonidine formulation. It is unfortunate that there is a paucity of Russian studies that directly compare the efficacy of Physiotens and its generic counterparts. For example, in subjects with pronounced BP elevation, Physiotens demonstrated a more pronounced and rapid antihypertensive effect than two generic comparators [2]. The findings of this study were confirmed in real-world clinical practice: a retrospective analysis of the organization of pre-hospital care for individuals with markedly elevated blood pressure revealed that original moxonidine exhibited comparable antihypertensive efficacy to intravenous urapidil administration [16]. Furthermore, the number of patients who responded to Physiotens was greater than that observed in the groups treated with generic drugs. In the study conducted by G.V. Ramenskaya et al, differences in dissolution kinetics were demonstrated for all moxonidine formulations of interest compared to the reference drug Physiotens [3]. The authors of this study suggested that Physiotens and the generics studied may have unequal clinical effects.

Conclusion

Inclusion of original moxonidine in combination antihypertensive pharmacotherapy in patients with uncontrolled hypertension allowed to reach the target BP values more quickly compared to generic drugs. A statistically significant decrease in office SBP, DBP, and HR, as well as more pronounced positive changes in 24-hour BP monitoring parameters, were observed during the administration of original moxonidine formulation compared to the administration of generic formulations. The number of patients exhibiting normalization of the 24-hour BP index was significantly higher in the group treated with the original drug than in the group treated with generic moxonidine formulations. A notable reduction in BMI was observed across all study groups, with a comparable magnitude of change.

The findings of our study can contribute to the clinical decision-making process when selecting an appropriate moxonidine for the treatment of patients with uncontrolled hypertension, including those with obesity and carbohydrate metabolism disorders.

Limitations

The study was conducted in a real-world clinical practice setting, with the investigator physicians independently determining patient eligibility and selecting the appropriate moxonidine formulation for each patient.

Conflict of interest

The authors state that there is no financial interest and participation
of companies in planning, conducting statistical processing of research results, as well as writing an article.

The article was received on 16/07/2024

ISSN 0022-9040. Kardiologiia. 2024;64(8). DOI: 10.18087/cardio.2024.8.n2731

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