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EFFECTIVENESS OF USING SULODEXIDE IN THE COMPLEX TREATMENT OF PATIENTS WITH ARTERIAL HYPERTENSION WITH ACCOMPANYING DIABETES MELLITUS IN THE POST-COVID PERIOD

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Aim. To study the effectiveness of using sulodexide in the complex treatment of patients with arterial hypertension with accompanying diabetes in the post-COVID period.

Methods. According to the inclusion criteria, 87 patients with hypertension and concomitanttype 2 diabetes participated in the study. Patients were included in the study after having COVID-19 at an average of 57.82±3.2 [46–112] days after the onset of infection. The first, main group, consisted of 45 patients who additionally used sulodexide capsules (250 LO twice a day for 3 weeks) against the background of the basic treatment of hypertension and diabetes. The second (control) group consisted of 44 patients, who received only the basic treatment of hypertension and diabetes.

Results. It was established that the use of sulodexide (250 LO twice a day for 3 weeks) in the complex treatment of patients with hypertension and diabetes in the post-COVID period compared to the control group was accompanied by a reliable disappearance or reduction of the symptoms of the post-COVID syndrome, an additional decrease in blood pressure, a significant decrease in the ankle-brachial index, which indicated improvement in peripheral blood circulation and quality of life of these patients.

Conclusions. Addition of sulodexide capsules to basic therapy in patients with hypertension and concomitant diabetes mellitus contributes to increasing the effectiveness of complex treatment, as evidenced by the reduction of symptoms of long post-COVID syndrome against the background of improvement in the course of comorbid pathology, improvement in the quality of life of patients.

Key words: arterial hypertension, diabetes mellitus, COVID-19, post-COVID period, sulodexide.

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ЕФЕКТИВНІСТЬ ВИКОРИСТАННЯ СУЛОДЕКСИДУ У КОМПЛЕКСНОМУ ЛІКУВАННІ ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ З СУПУТНІМ ЦУКРОВИМ ДІАБЕТОМ У ПОСТКОВІДНОМУ ПЕРІОДІ

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Метою дослідження було вивчити ефективність використання сулодексиду у комплексному лікуванні хворих на артеріальну гіпертензію (АГ) з супутнім цукровим діабетом (ЦД) у постковідному періоді. У дослідженні відповідно до критеріїв включення прийняли участь 87 пацієнтів, хворих на АГ із супутнім ЦД 2 типу. Пацієнти були включені до дослідження після перенесеного COVID-19 в середньому через 57,82 ± 3,2 [46–112] днів після початку інфекції. Середній вік становив 57,8 ±3,9 років.

Результати. Встановлено, що застосування сулодексиду (по 250 ЛО двічі на день протягом 3-х тижнів) у комплексному лікуванні пацієнтів з АГ та ЦД у постковідному періоді порівняно до контрольної групи супроводжувалось достовірним зменшенням проявів постковідного синдрому, покращанням периферичного кровообігу та показників якості життя цих пацієнтів.

Ключові слова: артеріальна гіпертензія, цукровий діабет, COVID-19, тривалий постковідний синдром, сулодексид.

Introduction. The combination of arterial hypertension (AH) and diabetes mellitus (DM), taking into account the common pathogenetic mechanisms of occurrence and progression, leads to a significant increase in micro- and macrovascular disorders and a risk increase of cardiovascular complications [1, 2].

The guidelines of the European Society of Cardiology (ESC) [3] and the European Society of Hypertension [4] recommend considering the presence of diabetes mellitus with or without target organ damage when classifying the stage of arterial hypertension.

It has been established that coronavirus disease 2019 (COVID-19) in patients with hypertension with accompanying diabetes mellitus causes deterioration of blood pressure (BP) control, functional state of the cardiovascular system (CVS), and deterioration of carbohydrate metabolism indicators, which persist in the post-COVID period [5, 6].

Long-lasting COVID is a clinical syndrome characterized by the persistence or development of

symptoms caused by COVID-19 for at least 4 to 12 weeks after the initial infection [7]. In the TUN-EndCOV study [8], patients with long post-COVID, most of whom had hypertension (in 36.9%) and diabetes mellitus (27.9%), were found to have long microvascular and endothelial dysfunction, which may explain the large number of symptoms of long COVID-19. In a subsequent publication [9], the authors demonstrated that the use of sulodexide in patients with long post-COVID syndrome (PCS) improves endothelial function and reduces symptoms provoked by COVID-19.

The above substantiates the relevance of further research on using sulodexide in the post-COVID period with this comorbid pathology.

The aim of the study was to investigate the efficacy of sulodexide in the complex treatment of patients with arterial hypertension with concomitant diabetes mellitus in the post-COVID period.

Materials and methods. It is an open comparative study with a prospective set of patients under inclusion and exclusion criteria. The study was conducted at the Center for Reconstructive and Restorative Medicine (University Clinic) of Odesa National Medical University (ONMedU) from November 2021 to December 2023. The study was carried out pursuant to the Protocol approved by the Commission on Bioethics of ONMedU (protocol No. 2/21 dated 18.10.2021) and conducted in accordance with the written consent of the participants and the principles of bioethics set forth in the Declaration of Helsinki "Ethical Principles of Medical Research Involving Humans" and "Universal Declaration of Bioethics and Human Rights (UNESCO)". Before inclusion in the study, patients gave informed written consent to participate in the study.

Following the inclusion criteria, 87 patients with arterial hypertension (AH) with concomitant type 2 diabetes mellitus (T2DM) who suffered from COVID-19 infection more than 4–12 weeks ago were included in the study. The mean age was (57.8 ±3.9) years.

The criteria for inclusion in the study were as follows: male and female patients aged 45–74 years, duration of hypertension and diabetes for at least a year, presence of symptoms of post-COVID syndrome or worsening of the general condition that last longer than 4–12 weeks after the coronavirus infection, signing of the informed consent to participate in the study. Among the 19 exclusion criteria, special attention was paid to decompensated chronic diseases and conditions with a life expectancy of less than 1 year, for women of childbearing age – pregnancy or breastfeeding, taking anticoagulants and known disorders of the blood coagulation system.

All patients underwent a comprehensive clinical examination, in which complaints were taken into account (their severity and duration, the relationship of symptom amplification with exercise, stress, dietary disorders); anamnestic data were analysed (duration of hypertension and diabetes mellitus, frequency of exacerbations, family history, etc.); information on other comorbidities, in particular COVID-19, was collected. Particular attention was paid to assessing the efficacy of drugs of basic therapy for hypertension and diabetes, the presence of allergies or intolerances to the drugs that patients were using, and patients' adherence to treatment in general.

The patients were divided into 2 groups depending on ttherapy. The first (main) group included 43 patients who additionally used sulodexide (VesselDue, Alfasigma Sp.A., Italy, 250 IU twice a day for 3 weeks) against the background of baseline therapy of AH and T2DM. The second (control) group included 44 patients, who received only the basic treatment of AH and T2DM. Information on COVID-19 infection was obtained from the outpatient records of patients who were treated as outpatients by a family physician and from the inpatient records of patients who were treated in a hospital setting.

Patients in both groups underwent general clinical examination at the first visit and 3 weeks later at the second visit, namely: collection of complaints and anamnesis with analysis of previous medical records, objective clinical examination, office blood pressure measurement. Anthropometric data (body weight, height, body mass index (BMI), waist circumference) were necessarily recorded. Body weight calculated with BMI was measured at each patient visit. In addition to the general clinical examination, the level of office blood pressure (BP office), ankle-brachial index ABI, home blood pressure monitoring (HBPM), electrocardiography (ECG), and transthoracic echocardiography (TTE) were analyzed in detail.

Verification of symptoms of post-COVID syndrome, which lasted longer than 4 weeks after the onset of the coronavirus disease, was carried out in accordance with the generalized recommendations of NICE, SIGN, and RCGP rapid guideline [7].

In all patients, the risk of the probability of developing cardiovascular complications within 10 years was calculated using the SCORE2 scale, in which patients with diabetes mellitus were included in the risk calculation [10].

Fatigue was assessed using a modified fatigue severity scale [11, 12]

Quality of life indicators of patients were assessed using the validated EQ-5D questionnaire developed by the European Quality of Life Research Group [13].

Statistical processing of the obtained data was carried out using Microsoft Excel 2013 (Microsoft Corporation, USA, 2013) and Statistica 6.0 (StatSoft, version 13.3.721) computer programs. Fisher's test was used to check the groups of the studied patients for normal distribution. In case of normal distribution, parametric methods of statistical processing of the obtained data were used. The average values were marked by M, the error by m. The indicators are given as the average value and the standard error of the average value (M ± m). The probability of the difference in indicators was calculated using the χ^2 test and Student's t-test with normal distribution of values. The results of comparison under conditions of $p<0.05$ were considered reliable [14].

Results and their discussion. 87 patients were randomized to the study after past COVID-19 on average in (57.82 ± 3.2) [46–112] days after the onset of the infection. The groups of patients who were divided into the main and control groups were approximately identical by age, gender, duration of hypertension, type 2 diabetes, and the post-COVID period (Table 1).

Table 1

Characteristics of patients with arterial hypertension with accompanying diabetes who were included in the study

Index	Group I (main) (n=43)	Group II (control) (n=44)	p
Age, M ± m, years	58.7 ± 3.9	56.8 ± 4.8	>0.05
Men, n, %	24 (55.8%)	25 (56.8%)	>0.05
SBP level, M ± m, mmHg	153.8 ± 3.7	159.8 ± 3.2	>0.05
DBP level, M ± m, mmHg	86.7 ± 4.1	89.3 ± 4.9	>0.05
Fasting glucose level, M ± m, mmol/l	8.9 ± 0.9	9.2 ± 1.1	>0.05
BMI (kg/m^2)	33.0 ± 3.3	29.3±2.7	>0.05
AH duration, M ± m, years	5.2 ± 0.9	4. 4 ± 1.1	>0.05
T2DM duration, M ± m, years	3.9 ± 0.9	4.1 ± 1.2	>0.05
Post-COVID period duration (M ± m, days)	54.9 ± 8.2	60.4 ± 7.8	>0.05
COVID-19, which required hospitalization (n, %)	9 (20.0)	11 (25.6)	>0.05

Notes: 1. Data of quantitative indicators are presented as (M ± m) – mean value ± mathematical error of the mean. 2. the comparison of percentages between groups was carried out using the χ^2 criterion 3. the difference was considered reliable at $p<0.05$. 4. AH is arterial hypertension. 5. BP – blood pressure. 6. DBP – diastolic blood pressure.7. BMI – body mass index. 8. SBP – systolic blood pressure. 9. T2DM– 2 type diabetes mellitus

The analysis showed that according to the main indicators of clinical characteristics, age, sex, duration of diseases, and the patients of both groups were comparable (Table 1).

The basic therapy of AH, following the international recommendations of ESC/ESH [3, 4], included the use of angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) in combination with a calcium channel blocker, amlodipine or hydrochlorothiazide. The proportion of patients who received double antihypertensive combinations of ACEI in combination with hydrochlorothiazide or amlodipine in the main group was 35.0%, in the control group – 33.3% ($p>0.05$), ARB in combination with hydrochlorothiazide or amlodipine in the main group was 45.0%, in the control group – 41.7% ($p>0.5$). The triple antihypertensive combination (ACEI or ARB in combination with hydrochlorothiazide and amlodipine in the main group was 20.0%, in the control group – 25.0% ($p>0.5$). Metformin was included in the basic therapy of DM 2 in most patients in combination with glimepiride (83.3% in the main group and 80.0% in the control group ($p>0.5$)). Triple combination of antidiabetic drugs, which included metformin in combination with glimepiride with the addition of dapagliflozin or empagliflozin, was received by 11.7%. patients of the main group and 13.3% of the control group ($p>0.5$)). Only 3 (0.5%) patients of the main group and 4 (0.7%) patients of the control group received metformin monotherapy ($p>0.5$). That is, in the main group and the comparison group, the composition of basic therapy for hypertension and diabetes was almost similar. 14 (23.3%) patients of the control group and 16 (26.7%) of the main group additionally received sulodexide capsules of 250 IU twice a day. All patients were also prescribed statin therapy with atorvastatin or rosuvastatin in mean therapeutic doses. All patients were also given recommendations for dosed physical activity, which are approved by the World Health Organization for patients who were ill with COVID-19 [15].

The majority of patients (78.2%) had symptoms of long post-COVID syndrome, which was already described earlier [5]. Most often, complaints of headache, cough, palpitations, and general weakness were registered in patients with this comorbid pathology.

After the correction of the complex treatment of hypertension and diabetes mellitus at the 2nd visit after 3 weeks, the patients of both groups, especially those who additionally received sulodexide, had reduction in symptoms of post-COVID syndrome (Table 2).

Table 2 shows that the patients of both groups suffering from hypertension with accompanying diabetes in the post-COVID period had a decrease in symptoms of post-COVID syndrome after treatment, especially the patients of the main group. However, the patients who used sulodexide had a significant decrease in complaints of increased fatigue, general weakness, sweating, and muscle pain. It should be emphasized that when using sulodexide in the complex therapy of this comorbid pathology in patients included in the study, in all cases no side effects or violations of clinical and laboratory parameters were observed.

In patients with arterial hypertension and concomitant diabetes mellitus, 32 (74.4%) people in the main group and 34 (77.3%) people in the control group ($p>0.05$) had uncontrolled arterial hypertension in the post-convulsive period, which was reflected in the blood pressure indicators in the middle groups regardless of whether the patients took antihypertensive drugs. In both groups, 3 weeks after treatment correction, a decrease in blood pressure was observed, but this decrease was significant only in the main group (Table 3).

In the group of patients in which sulodexide was used in the complex treatment, an improvement in peripheral blood circulation was also observed, which was reflected in a significant increase in ABI in the main group (Table 3).

The additional reduction in blood pressure and improvement in peripheral circulation in patients of the main group can be explained by the fact that sulodexide has an endothelium-modulating effect. Our data confirm the results of the study [9], in which the inclusion of sulodexide capsules in the complex therapy of patients who had signs of reduce the symptoms of post-COVID syndrome and improve endothelial function.

Table 2

The frequency of detection of symptoms of long post-COVID syndrome in patients with arterial hypertension and concomitant diabetes mellitus after complex treatment (n, %, p)

Indices	Group I (main) (n=43)		p	Group II (control) (n=44)		p
	1st visit	2nd visit		1st visit	2nd visit	
Headache	24 (55.8%)	5 (11.6%)	<0.001	27 (61.4%)	9 (20.5%)	<0.001
Cough	19 (44.2%)	12 (27.9%)	0.10	21 (47.7%)	14 (31.8%)	0.11
Fatigue, general weakness	38 (88.4%)	11 (25.6%)	<0.001	40 (90.9%)	34 (77.3%)	0.08
Muscle and joint pain	12 (27.9%)	3 (6.9%)	0.011	14 (31.8%)	11 (25.0%)	0.44
Sweating	11 (25.6%)	4 (9.3%)	0.047	13 (29.6%)	8 (18.2%)	0.210
Smell disorder	21 (48.8%)	17 (39.5%)	0.34	24 (54.6%)	22 (50.0%)	0.67
Taste disorder	8 (18.6%)	8 (18.6%)	-	7 (15.9%)	6 (13.6%)	0.76
Sleep disorder	22 (51.2%)	11 (25.6%)	0.015	23 (52.3%)	18 (40.9%)	0.29
Patients having 1 PCS symptom	33 (76.7%)	14 (32.6%)	<0.001	37 (79.6%)	21 (47.7%)	<0.001
Patients having 2 or more PCS symptoms	14 (32.6%)	3 (6.9%)	0.003	15 (34.1%)	12 (27.3%)	0.026

Notes. 1. comparison of percentages between groups was carried out by the χ^2 criterion. 2. the difference was considered reliable at $p<0.05$. 3. PCS – post-COVID syndrome.

Table 3

Changes in blood pressure indices and ankle-brachial index in patients with arterial hypertension combined with diabetes mellitus depending on the type of treatment, M±m,

Indices	Main group, n=43	p	Control group, n=44	p
SBP, mmHg: visit 1 visit 2	 153.8 ± 3.7 134.2 ± 4.2	<0.05	 159.8 ± 3.2 144.6 ± 5.9	>0.5
DBP, mmHg: visit 1 visit 2	 86.7 ± 4.1 79.8 ± 4.4	<0.05	 89.3 ± 4.9 87.8 ± 5.6	>0.05
ABI on the left: visit 1 visit 2	 0.74±0.05 0.89±0.04	<0.01	 0.76±0.07* 0.82±0.05	>0.05
ABI on the right: visit 1 visit 2	 0.75±0.04 0.86±0.05	<0.05	 0.76±0.06* 0.81±0.04	>0.05

Notes:
1. ABI – ankle-brachial index.
2. DBP – diastolic blood pressure.
3. SBP – systolic blood pressure.
The reliability of the difference in indicators between the 1st and 2nd visits of each group is indicated by p.

The analysis of the hypoglycemic therapy effectiveness showed that after 3 weeks of treatment, the target fasting glucose level (less than 7.0 mmol/l) in the main group was achieved in a significantly greater number of patients compared to the control group (respectively, in (44.2±7.6)% of patients against (20.5±6.1)%, $p<0.01$).

The disappearance or reduction in the severity of symptoms of long post-COVID syndrome, a decrease in blood pressure, and an improvement in peripheral hemodynamics resulted in an improvement in the quality of life (EQ-5D questionnaire) of patients. In particular, in the main group, the integrated quality of life index increased from (46.4±6.1) to (65.3±5.4) points ($p<0.05$), and in the control group, not so significantly – from (47.8±4.8) to (59.1±5.6) points ($p>0.05$).

Therefore, after suffering from COVID-19, many patients continue to experience symptoms of long post-COVID syndrome, and the course of hypertension with concomitant diabetes mellitus worsens, which significantly affects the quality of life of these patients. It was established that the use of sulodexide in the complex treatment of patients with hypertension and diabetes in the post-COVID period, compared to the control group, was accompanied by a reliable disappearance or reduction of the manifestations

of the post-COVID syndrome, an additional decrease in blood pressure, an improvement in peripheral blood circulation, which was manifested by a reliable increase in the ankle-brachial index, an improvement of the quality of life indicators.

Conclusions. Addition of sulodexide capsules to basic therapy of patients with hypertension and concomitant diabetes mellitus contributes to increasing the effectiveness of complex treatment, as evidenced by the reduction of symptoms of long post-COVID syndrome against the background of improvement in the course of comorbid pathology, improvement in the quality of life of patients.

Prospects for further research

Studies of the optimal dosage and duration of sulodexide use in comorbid pathology, in particular in hypertension and diabetes mellitus, combined macro- and microvascular disorders, in patients with other cardiovascular pathology are considered promising.

Conflict of interest. The authors emphasize the absence of a conflict of interest.

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