

EFFECTIVENESS OF TREATMENT WITH MEBICAR IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION

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Abstract

Violation of the heart rhythm is widespread at present. Anxiety-depressive symptoms and a tendency to chronic stress leads to the depletion of the body, which contributes to arrhythmia.

The aim of the study is to assess the severity of clinical and hemodynamic indices by using anxiolytic drug mebicar.

Materials and methods. Assessment of psycho-emotional status was studied using the psychosocial scale of stress by L. Reader, PSS-10 PHQ-15 and questionnaire identification of social factors that can affect health. Determination of cortisol level in serum was carried out by immunoassay (ELISA) on the ER-500 Microplate Reader. The concentration of N-terminal fragment of the brain natriuretic peptide precursor (NTproBNP) in serum was determined by ELISA using a Biosan PST-60HL shaker.

Results. The results of the survey showed a direct dependence of the manifestation of atrial fibrillation (AF) on the level of psychoemotional stress. We found that in group 1b (standard treatment+mebicar) there were complaints of increased excitability ($p<0.001$), (p-reliability difference of indices before and after treatment), fatigue ($p<0.001$), deterioration of memory ($p<0.01$), appetite loss ($p<0.05$), sleep disturbance ($p<0.001$), signs of severe sweating ($p<0.001$), indicating the appearance of astheno-vegetative syndrome. The reduction of manifestations of high stress ($p<0.01$) in patients of group 1b (standard treatment+mebicar) was noted. A similar pattern was detected in the severity of anxiety in men ($p<0.01$).

Conclusions. Application in the complex therapy of patients with stable coronary heart disease (SIHD) in conjunction with AF anxiolytics of the benzodiazepine series (mebicar) has allowed stopping anxiety-depressive disorders. Analyzing the level of cortisol, we observed its increase depending on the degree of anxiety and depression; NT-proBNT metrics are respectively.

Keywords: atrial fibrillation, stress, cortisol, mebicar, N-terminal fragment of the precursor of the brain natriuretic peptide (NTproBNP).

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1 Introduction

Atrial fibrillation (AF) is the most commonly persistent cardiac arrhythmia in clinical practice, which contributes to a deterioration in the quality of life, increased morbidity and mortality [1]. Anticipated by 2030 due to risk factors such as obesity and diabetes [2], arrhythmia [3], arterial hypertension [4], more than 23,3 million people will die from acute myocardial infarction (MI), stroke, [2] systemic embolism [3] and life-threatening cardiovascular disorders [5].

Among the population of Ukraine, cardiovascular disease (CVD) accounts for 63.3 % of all fatal cases [6]. Significant groups of the population have mental disorders, including post-traumatic stress disorder (PTSD) and disorders of adaptation. Their prevalence in the population is: PTSD – 1–3 %, adaptive disorders – 5–20 % of all patients. In the structure of morbidity, non-psychotic mental disorders prevail – neuroses, reactions to stress, personality disorders [7].

Anxiety-depressive symptoms [5], negative emotions [8], and the impact of chronic stress were considered by cardiologists and psychiatrists a long time ago [9]. For many decades, the theory of psychosomatic heart disease has been formed [9]. Clinical trials have been conducted to study the role of depression, anger, anxiety and chronic stress with AF incidents. MESA (Multi-Ethnic Study of Atherosclerosis) has confirmed the association of anxiety-depressive states with an increased risk of AF [10, 11]. Therefore, there is a relationship between AF and these states [12], but the spectrum of psychological disorders remains unclear [13].

As a rule, stress-induced rhythm disturbance is manifested by tachyarrhythmias characterized by a pathologically rapid rhythm. Conditionally, they can be divided into organic-associated with any pathology of the heart muscle or vessels, most often it is SIHD, myocardial infarction, myocarditis, cardiosclerosis, cardiomyopathies and inorganic (functional) – have no basis for organic lesions, the main causes of their development there are physical and psychological overload, emotional shock, frequent stress situations, intoxication, hypoxia, alcohol, smoking [9].

It is suggested that personal psychology and the presence of psychological distress may be due to the influence on the sympathetic nervous system, systemic and regional inflammation, and the endothelium function to be factors contributing to the development of AF [13]. The interaction of the cardiovascular and nervous system is a complicated algorithm in a state of rest, and in the period of stress these reactions become even more complex and dynamic. Negative emotions lead to coronary ischemia, platelet activation, changes in hemodynamics and the release of catecholamines in the blood, as well as cause electrical dissociation in the atria and ventricles [9].

The mechanisms underlying both initiation and the onset of AF are not sufficiently established, but they are believed to include inflammation and oxidative stress [1]. There is a strong evidence that there is a strong correlation between inflammation and the pathogenesis of AF [1, 3]. Various inflammatory markers (C-reactive protein, tumor necrosis factor-, interleukin-2, interleukin-6, interleukin-8) were associated with AF. These include the activation and damage of the endothelium, the production of tissue factor from monocytes, increased platelet activation and fibrinogen expression [3]. Oxidative stress is characterized the inability of the cell to overcome the increase in the release of reactive oxygen species and prevent damage to cellular structures as a result of this increase. Excessive development of which can lead to damage to the oxidative tissue of the myocardium.

Natriuretic peptide B-type (BNP) is synthesized by ventricular cardiomyocytes in the form of preproBNP precursor proteins. The main stimulus of its secretion is increased pressure of the myocardium with increasing pressure in the left ventricle of the heart. Subsequently, preproBNP is cleaved and released into the blood in the form of N terminal fragment – NTproBNP and active hormone – BNP. High concentration and stability in serum allows using NTproBNP to evaluate the function of the myocardium [2]. Investigated the content of glucocorticoid hormones in biological fluids, which are objective criteria for the level of acute stress and the type of response of the body to the psycho-emotional stress. After all, psycho-emotional stress is associated with an increased content of cortisol, which is associated with anxiety-depressive symptoms [8]. Violation of adequate interaction between the cardiac muscle and the above listed structures in response to emotional stress increases the risk of arrhythmia and sudden cardiac death [9].

Therefore, the main task is correction of pharmacological and psychotherapeutic methods of treatment. One of the few drugs that meets these needs is a mebicar, which is used in clinical practice. It has a wide clinical and pharmacological spectrum of action, suppresses feelings of fear, emotional tension, anxiety and anxiety, improve memory and intellectual activity. Daily dosage – 500 mg twice a day, regardless of food intake [11].

The aim of research is to evaluate the effectiveness of treatment with mebicar in patients with permanent atrial fibrillation.

2. Materials and methods

31 medical records of patients undergoing treatment at the cardiology department of the regional clinical cardiology center in Ivano-Frankivsk were examined. All patients were divided into 2 groups: 1a – patients with SIHD with a constant form of AF who received standard therapy (16 patients were examined), 1b – patients with SIHD with permanent form of AF form that had anxiolytic therapy in the complex treatment (15 patients were examined). Prior to treatment, the groups did not differ from each other, during controlled treatment, the standard treatment group

received antihypertensive therapy (angiotensin-converting enzyme inhibitor or sartans), anticoagulant therapy (warfarin, dabigatran), β -blockers (bisoprolol, metoprolol, nebivolol), lipid-lowering drugs (statins), and in group 1b, in addition to standard therapy, mebicar was prescribed twice daily during the treatment period. The duration of controlled follow-up lasted 2 weeks. The study was conducted from February 26, 2018 to January 28, 2019.

Criteria for inclusion in the study: signed informed consent to participate in the study; permanent form of AF, documented on an electrocardiogram (ECG). Criteria for exclusion from the study: incapable patients for the psycho-neurological condition; acute conditions (acute coronary syndrome, myocarditis, pulmonary artery thromboembolism, life-threatening rhythm disturbances (persistent ventricular tachycardia, ventricular fibrillation); reversible causes of AF, such as thyrotoxicosis, alcohol intoxication.

All surveyed signed informed consent to participate in the study in accordance with the World Health Association Declaration of Helsinki. The study was approved by the Commission on Ethical Principles of Ivano-Frankivsk National Medical University No. 120/20 from 21.05.20.

All surveyed were evaluated for stress according to the methodology of the psychosocial stress scale by L. Reeder. Questionnaire of L. Reeder included 7 questions and 4 possible answers to each question. The level of stress was assessed as low (0.00–0.99 points), mean (1.00–1.99 points) and high (2.00–3.00 points) stress in men and women (0.00–1.17 points), (1.18–2.17 points) and (2.18–3.00 points), respectively. The scale of perceived stress – 10, included 10 points, divided by the level of stress, where 0–13 corresponds to the position “low”, 14–16 – “medium”, and 27–40 – “high”. The PHQ-15 consists of 15 points that are used to diagnose somatoform disorder. The questionnaire for identifying social factors that may affect health includes 28 points. Hospital scale HADS was used to assess the degree of anxiety and depression. The questionnaire for the detection of the status of anxiety and depression presented 7 questions with 3 variants of the answer. Interpretation of these results allows to differentiate 3 categories of the state: norm, subclinical and clinical level. 0–7 points – norm, no dealings; 8–10 – possible case of anxiety/depression; 11 or more is a likely case of anxiety/depression.

Quantitative determination of catalase by A. Bach and S. Zubkova was carried out by titration using hydrogen peroxide, sulfuric acid, potassium permanganate, distilled water and patient blood. The activity of superoxide dismutase was determined on the device KFK-2MP device, the principle of determination is based on the establishment of nitrotetrazole by superoxide radicals formed by the reaction between phenazine metasulfate and a certain form of nicotinamide dinucleotide. Reagents used for this purpose: 0.15 M phosphate buffer (pH 7.8), incubation mixture – 37 ml of EDTA- Na_2 (ethylenediaminetetraacetate disodium salt), 330 ml of nitrotetrazole blue, 55 ml of phenazine metasulfate. This mixture was mixed with 300 ml of phosphate buffer and left overnight, filtered in the morning. The calculation was performed according to the formula:

$$\text{SOD (\%)} = \frac{E_k - E_0}{E_k} \times 100.$$

The activity of glutathione peroxidase (GP) was determined on an apparatus on SPE-CORDM40, using a reaction mixture comprising - 1 ml of phosphate buffer, azide Na 12 mm – 0.9 ml, 0.5 ml – 2.5 mm reduced glutathione, 0.2 ml of serum of the patient's blood, 0.5 ml of H_2O_2 . The reaction was started by adding H_2O_2 , stopped after 2 minutes by adding 1 ml of 10 % trichloroacetic acid. Centrifuge at 3000 rpm for 15 minutes. Determined the extinction of oxidized glutathione at 260 nm. The enzyme activity was expressed in micromoles of oxidized glutathione per 1 g Hb per minute.

The quantitative determination of the concentration of total cortisol in serum was determined by ELISA using the ER-500 Microplate Reader. Reagent kit 3625–300 Cortisol Test System, Monobind Inc., USA. The set of reagents included: calibrators cortisol – 1 ml/vials, enzyme reagent cortisol – 1.0 ml/vials, steroid conjugate buffer – 7.0 ml/vials, streptavidin-coated plate, wash solution concentrate – 20 ml, substrate A – 7 ml/vials, substrate B – 7 ml/vials, stop solution –

8 ml/vials. Reagents required for a solid-phase enzyme-linked immunosorbent assay include antibodies, an enzyme conjugate with antigen and a native antigen. When mixing biotinylated antibodies, the enzyme-antigen conjugate and the native antigen contained in the serum, there is a competition between the native antigen of the sample and the enzyme-antigen conjugate for a limited number of immobilized binding sites.

The content of N-terminal fragment concentration of the brain natriuretic peptide precursor (NTproBNP) in serum was determined by ELISA using a SINNOWAER-500 spectrophotometric analyzer using a Biosan PST-60HL shaker. Catalog number is A-9102. The firm – the manufacturer – BEST (Russia). The set includes calibration samples K_1 , K_2 , K_3 , K_4 and K_5 based on human serum, certified against the standard «Liquichek Cardiac Markers Plus Control» (firm BioRad, France), contain known amounts of NTproBNP; control sample based on human serum with known content NTproBNP, lyophilized – 1 bottle; conjugate of monoclonal antibodies to NTproBNP with horseradish peroxidase, concentrate-1 vial (0.7); dilution solution samples – 1 vial (12.0 ml); solution for diluting the conjugate – 1 vial (13.0 ml); serum dilution solution – 1 vial (12.0 ml); 25-fold concentrate of phosphate-buffered saline with twin (FSB-T25) – 1 vial (12.0 ml); tetramethylbenzidine plus solution (TMB plus solution), ready to use – 1 vial (12.0 ml); ready-to-use stop reagent – 1 vial (12.0 ml).

The statistical analysis of the results was carried out using the STATISTICA-10 program. The presence of differences between the studied indicators was assessed by Student's test.

3. Results

A study conducted among patients with a permanent form of AF found that the risk of mental disorders in the absence of preventive and corrective measures increases significantly. Clinical manifestations occur within a month after a stressful situation, and the duration of symptoms does not exceed 6 months. Patients complained of general anxiety and dissatisfaction with life, making impulsive, ill-considered decisions. Irritability, increased fear, aggression, attacks of unfounded anger were noted. Impaired concentration and memory, poor performance, uncontrolled emotions, depression, and loss of desire to do something and strive for something.

After conducting a clinical examination in the relevant groups, we obtained the following results. Adaptation disorders (**Table 1**) in patients of group 1b with a high level of anxiety and depressive symptoms were characterized by astheno-vegetative syndrome. Analysis of the results confirmed signs of irritability ($p<0.001$), memory impairment ($p<0.01$), sleep disturbances ($p<0.001$), loss of appetite ($p<0.05$), signs of severe sweating ($p<0.01$), fatigue ($p<0.001$), which confirms the reliability of these indicators. It was noted that patients complained of intermittent sensations, rapid heartbeat, chest pain, which corresponded to the clinical picture of atrial fibrillation. In addition, in both study groups, the frequency of complaints of headache decreased from 75.0 % and 80.0 % of cases, up to the absence of manifestations ($p<0.001$). According to the objective examination, we found that in patients of both groups the symptoms corresponded to heart failure, due to shortness of breath at rest, edema of the lower extremities and acrocyanosis.

Against the background of psychopharmacotherapy, patients noted the normalization of mood, improved sleep, recovery, recovery of interest in work, reducing the manifestations of astheno-autonomic syndrome. Therefore, after analyzing the clinical picture, we can say that the commitment to treatment with mebicar in patients of group 1b is reliably confirmed.

Comparison of the obtained data showed that in the group of patients receiving standard treatment in comparison with the group receiving mebicar in addition there were more people with low stress (43.75 % and 6.67 %, respectively, $p>0.05$). The level of high stress decreased significantly ($p<0.001$), respectively, the number of patients with moderate stress increased ($p<0.01$). It is interesting to note that among men signs of acute (divorce, death or serious illness of a loved one, lawsuit against a family member) and chronic (serious financial problems, long-term difficult relationship with a woman or children) psychosocial stress were much more common than among women (**Table 2**).

Table 1

Clinical indices in patients with a permanent form of AF

Indicators	Standard therapy 1a group (n=16)		Standard therapy + mebicar 1b group (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
The feeling of interruptions	15 (93.75 %)	9 (56.25 %) p<0.05	10 (66.67 %)	1 (6.67 %) p<0.001
Accelerated heartbeat	10 (62.50 %)	5 (31.25 %) p>0.05	7 (46.67 %)	1 (6.67 %) p<0.001
Shortness of breath at rest	4 (25.0 %)	— p<0.05	5 (33.33 %)	— p<0.001
Chest pain	5 (31.25 %)	— p<0.05	6 (40.00 %)	1 (6.67 %) p<0.001
Increase blood pressure	8 (50.0 %)	2 (12.50 %) p<0.05	7 (46.67 %)	— p<0.01
Fatigue	13 (81.25 %)	8 (50.0 %) p>0.05	15 (100.0 %)	7 (46.67 %) p<0.001
Increased excitability	—	1 (6.25 %) p>0.05	10 (66.67 %)	1 (6.67 %) p<0.001
Deterioration of memory	2 (12.50 %)	1 (6.25 %) p>0.05	7 (46.67 %)	— p<0.01
Frequent headaches	12 (75.0 %)	— p<0.001	12 (80.00 %)	— p<0.01
Loss of appetite	2 (12.50 %)	— p>0.05	5 (33.33 %)	— p<0.05
Sleep disturbance	5 (31.25 %)	1 (6.25 %) p>0.05	13 (86.67 %)	1 (6.67 %) p<0.001
Sweating	5 (31.25 %)	— p<0.05	10 (66.67 %)	— p<0.001
Acrocyanosis	4 (25.0 %)	— p<0.05	1 (6.67 %)	0 (0.00 %) p>0.05
Edema of the lower extremities (pastoseness)	13 (81.25 %)	— p<0.001	15 (100.0 %)	— p<0.001

Note: p – the reliability of the difference in indicators before and after treatment

Table 2

Indicators of psychosocial stress L.Rider in patients with a permanent form of AF

Level stress, points	Standard therapy 1a group (n=16)		Standard therapy + mebicar 1b group (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Low	7 (43.75 %)	4 (25.0 %) p>0.05	1 (6.67 %)	1 (6.67 %) p>0.05
Average	4 (25.0 %)	7 (43.75 %) p>0.05	7 (46.67 %)	14 (93.33 %) p<0.01
High	5 (31.25 %)	5 (31.25 %) p>0.05	9 (60.0 %)	0 (0.00 %) p<0.001

Note: p – the reliability of the difference between the indicators before and after treatment

According to the obtained data of the scale of perceived stress – 10, a high level of stress was diagnosed in 8 (53.33 %) persons of group 1b ($p<0.01$) compared with group 1a. Subjects in this group are characterized by increased levels of anxiety, internal conflict, lack of awareness and frequent stressful situations. Patients in group 1b after 2 weeks of regular use of mebicar managed to relieve stress symptoms ($p<0.01$) (**Table 3**).

Table 3

Indicators of perceived stress-10 in patients with a permanent form of AF

Level stress, points	Standard therapy (n=16)		Standard therapy + mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Low	0 (0.00 %)	0 (18.75 %) $p>0.05$	0 (0.00 %)	0 (0.00 %) $p>0.05$
Average	14 (87.50 %)	15 (93.75 %) $p>0.05$	7 (46.67 %)	14 (93.33 %) $p<0.01$
High	2 (12.50 %)	1 (6.25 %) >0.05	8 (53.33 %)	1 (6.67 %) $p<0.01$

Note: p – the reliability of the difference between the indicators before and after treatment

The HADS hospital scale, along with the assessment of the level of anxiety, allows to determine the level of depression (**Table 4**). In the examined cohort in 11 (73.33 %) patients with a permanent form of AF who received mebicar at the time of the questionnaire there was clinically pronounced anxiety ($p<0.001$) and depression ($p>0.05$). In 7 (43.75 %) persons of group 1a and in 1 (6.67 %) persons of group 1b the absence of anxiety was noted ($p>0.05$). In patients of group 1b there was a reduction in anxiety, from clinical to subclinical level ($p<0.001$), which explains the positive dynamics of treatment with mebicar.

Table 4

Indicators of the hospital scale of anxiety and depression of HADS in patients with a permanent form of AF

Criteria for assessing, score	Standard therapy (n=16)		Standard therapy + mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder anxiety (norm 0–7 points)	7 (43.75 %)	10 (62.50 %) $p>0.05$	1 (6.67 %)	2 (13.33 %) $p<0.05$
Subclinical level anxiety (possible case) (8–10)	6 (37.50 %)	5 (31.25 %) $p>0.05$	3 (20.0 %)	12 (80.0 %) $p<0.001$
Clinical level anxiety (probable case) (11 or more)	3 (18.75 %)	1 (6.25 %) $p>0.05$	11 (73.33 %)	1 (6.67 %) $p<0.001$
Absence of disorder depression (norm 0–7 points)	3 (18.75 %)	8 (50.0 %) $p>0.05$	1 (6.67 %)	4 (26.67 %) $p>0.05$
Subclinical level depression (possible case) (8–10)	7 (43.75 %)	8 (50.0 %) $p>0.05$	3 (20.0 %)	4 (26.67 %) $p>0.05$
Clinical level depression (probable case) (11 or more)	4 (25.0 %)	0 (0.00 %) $p<0.05$	11 (73.33 %)	7 (46.67 %) $p>0.05$

Note: p – the reliability of the difference between the indicators before and after treatment

When evaluating the PHQ-15 health questionnaire (**Tab. 5**) among patients receiving standard therapy, the absence of disorder and mild somatization disorder was found in 1 (6.25 %) and 10 (62.50 %) persons ($p>0.05$), while in patients taking mebicar this was not observed ($p<0.001$).

However, this group was dominated by moderate and severe somatization disorder in 11 (73.33 %) and 4 (26.67 %) people, respectively. Due to the treatment, the proportion of people with these disorders decreased to a mild level ($p<0.001$). Thus, we emphasize the connection between psycho-emotional disorders and cardiovascular pathology: the higher the level of anxiety and depressive symptoms, the worse the health of patients.

Table 5

Indicators of the PHQ-15 health questionnaire in patients with a permanent form of AF

Criteria for assessing health status, points	Standard therapy (n=16)		Standard therapy + mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (0–4)	1 (6.25 %)	5 (31.25 %) $p>0.05$	0 (0.00 %)	1 (6.67 %) $p>0.05$
Light somatization disorder (5–9)	10 (62.50 %)	11 (68.75 %) $p>0.05$	0 (0.00 %)	14 (93.33 %) $p<0.001$
Moderate somatosis disorder (10–14)	4 (25.0 %)	0 (0.00 %) $p<0.05$	11 (73.33 %)	0 (0.00 %) $p<0.001$
Severe somatization disorder (15+)	1 (6.25 %)	0 (0.00 %) $p>0.05$	4 (26.67 %)	0 (0.00 %) $p<0.05$

Note: p – the reliability of the difference between the indicators before and after treatment

The role of social factors, including the influence of the media, political events in the group of patients with psycho-emotional symptoms (**Table 6**).

Table 6

Indicators that may affect the health of patients with permanent AF

Indexes	Standard therapy (n=16)		Standard therapy + mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Deterioration of mutual understanding	3 (18.75 %)	1 (6.25 %) $p>0.05$	4 (26.67 %)	7 (46.67 %) $p>0.05$
Reduction of time of joint carrying out	0 (0.00 %)	3 (18.75 %) $p>0.05$	4 (26.67 %)	2 (13.33 %) $p>0.05$
The influence of the media	6 (37.50 %)	8 (50.0 %) $p>0.05$	12 (80.0 %)	5 (33.33 %) $p<0.01$
Political events	12 (75.00 %)	10 (62.50 %) $p>0.05$	10 (66.67 %)	2 (13.33 %) $p<0.01$

Note: p – the reliability of the difference between the indicators before and after treatment

As we can see, the activity of catalase was increased in two groups of patients (15.21 ± 1.29 and 8.74 ± 1.91 mg H_2O_2 /1 ml of blood) ($p<0.05$) and (17.67 ± 1.50 and 11.11 ± 2.08 mg H_2O_2 /1ml of blood) ($p<0.05$) compared with the norm ($9.52\text{--}12.92$ mg H_2O_2 /1ml of blood). When comparing serum superoxide dismutase data, the indicator is statistically higher ($p<0.05$) and is (49.87 ± 1.59 %) and (37.80 ± 5.37 %) ($p<0.01$), indicating inhibition of the activity of antioxidant enzymes. After our treatment, the activity of catalase and superoxide dismutase decreased in the respective study group. We found a high level of glutathione peroxidase activity in patients receiving anxiolytic therapy, in which the average value is 0.19 ± 0.02 mmlol/min/mg, whereas in patients receiving standard therapy, the rate was 0.15 ± 0.04 mmlol/min/mg ($p<0.05$). Taking into account the data of the spectrophotometric method and the titration method, it should be noted that the higher the anxiety-depressive symptoms, the higher the rates of free radical oxidation are (**Table 7**).

Table 7

Indicators of activity of catalase, glutathione peroxidase (GP), superoxide dismutase (SOD) of blood serum in patients with permanent form of AF

Indexes	Standard therapy (n=16)		Standard therapy + mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Catalase, mg H ₂ O ₂ /1ml of blood	15.21±1.29	8.74±1.91 p<0.05	17.67±1.50	11.11±2.08 p<0.05
SOD, %	34.81±4.03	27.13±6.04 p<0.05	49.87±1.59	37.80±5.37 p<0.01
GP, mmlol, min/mg	0.15± 0.02	0.15±0.04 p>0.05	0.19±0.02	0.16±0.03 p>0.05

Note: p – the reliability of the difference between the indicators before and after treatment

Analyzing the levels of cortisol (**Table 8**), we observed an increase in it, depending on the level of anxiety-depressive symptoms and stress susceptibility. In patients 1b, this figure is 20.18±3.79 µg/dl and 11.99±1.12 µg/dl (p<0.05), which indicates an increased degree of psycho-emotional stress. Thus, we see that the higher the level of psychological stress, the higher the rate of total serum cortisol compared to the standard treatment group (p>0.05).

Table 8

Dynamics of serum cortisol index in patients with permanent form of AF in the process of treatment with mebicar

Indexes	Standard therapy (n=16)		Standard therapy + mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Cortisol, µg/dL	11.71±1.53	10.59±2.00 p>0.05	20.18±3.79	11.99±1.12 p<0.05

Note: p – the reliability of the difference between the indicators before and after treatment

As shown by enzyme-linked immunosorbent assay, the tendency to increase NT-proBNP is not observed (**Table 9**). However, it was found that in the group of patients with anxiety and depressive symptoms, the level of NT-proBNP increased from 21.29±1.29 to 26.74±4.91 ng/ml (p>0.05), whereas in the standard treatment group this was not observed. When evaluating NT-proBNP digital data, it should be borne in mind that mebicar does not affect the manifestations of heart failure.

Table 9

Indicator of natriuretic peptide (BNP) and the N-terminal fragment of the precursor of the brain natriuretic peptide in serum (NT-proBNP) in patients with a permanent form of AF

Indexes	Standard therapy (n=16)		Standard therapy+ mebicar (n=15)	
	Before treatment	After treatment	Before treatment	After treatment
Natriuretic peptide (BNP) and N-terminal fragment of serum sodium natriuretic peptide precursor (NT-proBNP), ng /ml.	21.58±1.58	21.82±1.82 p>0.05	21.29±1.29	26.74±4.91 p>0.05

Note: p – the reliability of the difference between the indicators before and after treatment

5. Discussion

The results of multicenter studies confirm that the prevalence of new AF cases doubles every year and is 1.5 times higher in men than in women [15, 16]. It has been established that

70–80 % of patients with rhythm disturbance have borderline psychiatric disorders, in particular, anxiety and depression, which aggravate the course of AF [18]. The Framingham study demonstrated that tension, negative emotions are independent predictors of cardiovascular events [19, 20].

Among the prognostic markers of increased paroxysms of arrhythmia, an important role belongs to the symptoms of depressions, which is manifested by changes in psycho-emotional state [21–23]. These symptoms have been shown to increase the risk of death in patients, but the association with AF has been relatively limited [17].

According to the results of the study, the reception of a medical practitioner contributed to the reduction of anxiety-depressive symptoms and the level of psycho-emotional load, which creates a favorable course of the main disease. Thus, the changer we found in the spectrum of clinical and hemodynamic parameters established the relationship between psychopathological disorders and the constant from of atrial fibrillation.

Limitations of the study. The study was conducted during 2018–2019. The study included all patients older than 20 years old with the diagnosis of atrial fibrillation from February 2018 to February 2019.

The prospect for further research is the study of the relationship of psycho-emotional states on the development of paroxysm atrial fibrillation.

5. Conclusion

1. The inclusion of mebicar in the standard treatment of atrial fibrillation in patients with anxiety and depressive symptoms potentiates the manifestations of astheno-autonomic syndrome, helps reduce stress, anxiety and depression, promotes dynamics of stress with a decrease in the initial concentration of cortisol.

2. The use of mebicar in the treatment of patients with atrial fibrillation can reduce the violation of lipid peroxidation, blood levels of cortisol, which is clinically manifested by a positive correction of anxiety disorders and depression.

3. No significant effect of mebicar on the level of markers of heart failure in patients with atrial fibrillation was found.

Conflict of interest

The authors declare that they have no conflicts of interest.

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