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TREATMENT OPTIMISATION OF HEART FAILURE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND CONCOMITANT TYPE 2 DIABETES MELLITUS

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The course and consequences of acute myocardial infarction define concomitant diseases, particularly type 2 diabetes mellitus. The primary purpose was to estimate the efficiency of eplerenone in treating heart failure in patients with acute myocardial infarction and type 2 diabetes mellitus. Two groups and two subgroups were formed. Patients underwent general clinical examinations, troponin I, brain natriuretic peptide, and glycosylated hemoglobin. It was found that patients with myocardial infarction and type 2 diabetes mellitus have a significantly higher brain natriuretic peptide level in the blood. In using an optimized treatment scheme, a decrease in the level of the natriuretic peptide was noted in patients without diabetes during the third visit compared to the first and second. Significant differences in brain natriuretic peptide concentrations at different patient visits were found in patients with comorbidities (p=0.037). The appointment of eplerenone to standard therapy for patients with myocardial infarction with and without comorbid pathology has a positive effect on the efficiency of treatment and the course of heart failure, which is confirmed by a decrease in brain natriuretic peptide as one of the leading indicators of the effectiveness of treatment of heart failure progression.

Key words: acute myocardial infarction, type 2 diabetes mellitus, heart failure, brain natriuretic peptide, eplerenone.

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ОПТИМІЗАЦІЯ ЛІКУВАННЯ СЕРЦЕВОЇ НЕДОСТАТНОСТІ У ХВОРИХ НА ГОСТРИЙ ІНФАРКТ МІОКАРДА ІЗ СУПУТНІМ ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Перебіг та наслідки гострого інфаркта міокарда визначають супутні захворювання, зокрема цукровий діабет 2 типу. Мета – оцінка ефективності застосування еплеренону у лікуванні серцевої недостатності пацієнтів з гострим інфарктом міокарда та цукровим діабетом 2 типу. Сформовано дві групи та дві підгрупи у кожній. Пацієнтам проведено загальноклінічні обстеження, тропонін І, натрійуретичний пептид, глікозильований гемоглобін. Виявлено, що у пацієнтів із інфарктом міокарда та цукровим діабетом 2 типу значимо вищий рівень натрійуретичного пептиду в крові. При застосуванні оптимізованої схеми лікування відзначалося зниження рівня натрійуретичного пептиду в пацієнтів групи без цукрового діабету, під час третього візиту порівняно з першим та другим. У хворих з коморбідністю виявлені значущі відмінності концентрацій натрійуретичного пептиду на різних візитах пацієнта (p=0,037). Призначення до стандартної терапії еплеренону пацієнтам із інфарктом міокарда з коморбідною патологією та без неї здійснює позитивний вплив на ефективність лікування та перебіг серцевої недостатності, що підтверджується зменшенням показника натрійуретичного пептиду, як одного з головних показників ефективності лікування серцевої недостатності.

Ключові слова: гострий інфаркт міокарда, цукровий діабет 2 типу, серцева недостатність, натрійуретичний пептид, еплеренон.

The study is a fragment of the research project "Features of the cardiovascular pathology course in patients of different age categories, depending on the presence of the metabolic syndrome components and comorbid conditions, ways of detected disorders correction and prevention", state registration No. 0119U102864.

Cardiovascular disease continues to be the leading cause of death and disability worldwide. According to the World Health Organization, coronary heart disease (CHD) ranks primarily among the causes of death worldwide. In 2012, 18.7 million people died from cardiovascular diseases, of which 8.3 million – were due to CHD [4, 7].

The leading cause of immediate and long-term mortality from CHD is acute myocardial infarction (AMI), the course and consequences of which are affected by comorbidities, in particular type 2 diabetes mellitus (DM2), one of the frequent comorbid conditions in patients with AMI. International registries published between 2003 and 2018 show that diabetes mellitus accounted for 20–24 % of all AMI admissions [7, 12]. Hyperglycaemia is an independent predictor of the onset and progression of heart failure (HF) in patients with AMI and a history of DM2, particularly in those with preserved left ventricular ejection fraction (LV EF) [13]. The annual mortality rate in HF patients with preserved LV EF is about 5.2 %, and the leading cause is cardiovascular death [9]. The rate of hospital admissions due to decompensation in HF is comparable to that in patients with reduced LV EF [9].

The risk of death in AMI patients with diabetes mellitus is high, both in the acute period and for several years after AMI [12]. In AMI, hyperglycaemia leads to additional structural, functional and metabolic myocardial remodelling [13], and HF phenomena are more pronounced in these patients [7, 13]. The intracellular metabolic disorders and increased oxidative stress caused by hyperglycemia, insulin resistance and chronic inflammation are pathogenic mechanisms affecting LV dysfunction in DM2. These

mechanisms induce structural changes in the heart, such as LV hypertrophy and interstitial fibrosis, leading to the onset and progression of HF [13].

Currently, in Ukrainian and foreign literature, the question of finding and identifying haemodynamic parameters of predictive value in the development of HF in AMI patients remains open [5, 7].

Natriuretic peptides (NUPs) are one of the main biomarkers in HF [5, 8]. BNP is a member of the family of natriuretic peptides, including atrial natriuretic peptide (A-type, ANP, PNUP), brain natriuretic peptide (B-type BNP, BNP, MNUP), as well as C-type BNP (CNP) and D-type BNP (DNP). BNP is a biological marker of biomechanical stress. It retains its significance worldwide as a powerful tool for diagnosing acute and chronic HF, stratification of patients into high-risk groups of HF onset and progression, and as a predictor of treatment effectiveness and prognosis assessment [6, 8, 15]. The prognostic value of BNP has remained an independent predictor of all-cause mortality, cardiovascular death and rehospitalisation in patients with HF with reduced LV EF.

Mineralocorticoid receptor antagonists (MCRA) are widely used in patients with systolic HF, except in patients with preserved EF [10]. The use of MCRA may be indicated given fibrosis reduction and other pleiotropic effects, but there are no evidence-based data to this day, only occasionally few trials [8, 14].

Despite significant success in therapy over the last decade, mortality of AMI patients complicated with HF and concomitant DM2 is relatively high, and quality of life is often unsatisfactory, which has encouraged the search for new approaches to optimise early diagnosis and treatment of these comorbid diseases.

The purpose of the study was to evaluate eplerenone's efficacy in treating heart failure in patients with acute myocardial infarction and type 2 diabetes mellitus.

Material and methods. The study was performed based on CP Poltava Regional Clinical Cardiovascular Centre of Poltava Oblast Council (POCMC POR). Sixty men and women were included in the research. The median age was 65 (56; 74) years. Inclusion criteria: patients with AMI complicated by acute HF with preserved LV EF and concomitant DM2 without it. The class of acute HF was defined by the Killip-Kimbal classification [9]. The diagnosis of AMI was established according to the order of MHC of Ukraine No. 455 from 02.07.2014 and No.1936 from 14.09.2021 “Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) care” [1, 3].

The diagnosis of type 2 diabetes mellitus is determined by the joint recommendations of the American diabetes association and the European association for the study of diabetes – 2018 and the Unified clinical protocol of primary and secondary (specialized) medical care “T2DM” by order of the Ministry of Health of December 21, 2012, No. 1118 [2].

The diagnosis of HF was established according to the European Society of Cardiology Guidelines for the Diagnosis and Management of Acute and Chronic HF (2012) [7, 9].

Patients were divided into two study groups according to clinical diagnosis and two subgroups in each according to the chosen method of treatment:

– Group 1a (n=15) – patients with AMI complicated by HF who received standard therapy (ST);

– Group 1b (n=15) – patients with AMI complicated by CH who received ST + optimized treatment regimen with eplerenone (ST+EP);

– Group 2a (n=15) – patients with AMI complicated by CH and concomitant type 2 diabetes who received ST;

– Group 2b (n=15) – patients with AMI complicated by CH and concomitant type 2 diabetes who received ST+EP.

All patients had a general clinical examination, troponin I and CPK MB, BNP, and glycated hemoglobin.

To assess the efficacy of treatment, patients were observed for 3 visits. The first visit was during the stay in the Department of Interventional Cardiology with intensive care unit, Radiosurgery Unit and the CHD Department of POCMC POR during the acute period of myocardial infarction (up to 10 days), the second visit 3 months after treatment, the third visit after 6 months.

According to the guidelines of the American diabetes association, the European association for the study of diabetes and the Orders of the MHC of Ukraine of 1936; No. 455, ST was used to treat AMI patients, including vasodilators, low molecular weight heparins, disaggregators, beta-adrenoblockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, statins. Urgent coronary angiography (CAG) with stenting of the infarction vessel was performed in 91.7 % (n=55) of patients. CAG was not performed in 8.3 % (n=5) of patients who refused or had contraindications. DM2 (blood sugar ≥10 mmol/l) was treated with subcutaneous short-acting insulin and diet therapy.

Optimizing the treatment regimen consisted of combining ST AMI with MCRA – eplerenone, in a dose of 25 mg once a day; “Epletor” tablets 25 mg No.30, manufacturer PJSC NPC “Borschagovsky KHPZ”, Ukraine.

Statistical analysis was performed using IBM SPSS Statistic v.26.0 (IBM inc., USA). The normality of distribution was assessed using the Shapiro-Wilk test. Quantitative measures are presented as arithmetic mean (M) and standard deviation (m). Quantitative comparisons between the two groups were made using a t-test for unrelated groups. Comparisons of indices in dynamics were made with ANOVA one-way analysis of variance and for repeated measures with Bonferroni correction. A p-value of less than 0.05 was taken as critical.

Results of the study and their discussion. The BNP concentration in the blood in group 1 patients was 325.3±26.8 pg/mL; in group 2, it was 415.6±24.9 pg/mL. A higher level of BNP in blood was found to be significant in patients with AMI and DM2 (p=0.016). This indicates LV myocardial ischaemia, impaired myocardial structure and function, and confirms the negative impact of carbohydrate disorders on the course of HF, which is established by a significant worsening of BNP values in AMI patients with concomitant DM2. Comorbidity in AMI is responsible for the severity of HF and significantly (p<0.05) confirms the negative impact of DM2 on the development and prognosis of HF, so control of biological markers, both in the acute and post-infarction period, requires more careful attention. Dynamic assessment of the severity of HF in AMI patients treated with different drug therapy regimens, as measured by BNP, are presented in Table 1.

Table 1

Dynamics in the concentration of natriuretic peptide in the blood of patients with acute myocardial infarction during treatment, pg/mL

Visit	Group	
	Group 1a	Group 1b
First	323.13±15.66	327.98±17.76**
Second	318.44±23.92	321.48±22.10**
Third	314.38±12.98*	251.92±17.34

Note: * – p<0.05 compared with the optimised scheme, ** – p<0.05- compared with the third visit

Baseline BNP concentrations in both subgroups were at comparable levels and showed no statistically significant difference (p=0.718). However, Group 1a showed no statistically significant differences over the follow-up period with protocol-only treatment (p=0.662) due to the absence of specific drugs directly affecting this indicator. Inflammation and fibrosis of cardiomyocytes can reduce the flow of oxygen and nutrients with an increase in the pathological remodelling response. In AMI patients, increased aldosterone is accompanied by an oxidative burst in cardiac muscle and marked activation of CaM-kinase, leading to calcium overload in mitochondria, impaired energy production, which leads to cell death and development and progression of CHD, which in turn leads to increased BNP.

With the optimised treatment regimen, there was a statistically significant reduction in BNP levels in group 1b patients during the third visit compared to the first (p=0.032) and second (p=0.024) visits, indicating a positive effect of the optimised treatment regimen by reducing myocardial fibrosis and remodelling heart voids, this effect being due to lower BNP levels in group 1b. In patients with HF, intracardiac aldosterone release is increased. The correlation between intracardiac and serum aldosterone directly corresponds with the level of the N-terminal fragment of procollagen III, a biochemical marker of myocardial fibrosis. This suggests that aldosterone may function as a stimulator of cardiac fibrosis. Taking eplerenone reduces intracardiac aldosterone excretion, which reduces the severity of fibrosis and leads to lower serum BNP levels.

During the second visit, no statistically significant difference was found between group 1a and 1b patients treated with different treatments (p=0.328). However, at the third visit, the BNP level was much lower in group 1b patients (p=0.018). This proves the positive effect of the optimised treatment scheme in group 1b compared to ST AMI.

The evaluation of HF for BNP data in group 2 over the course of treatment is shown in Table 2.

As in group 1a, group 2a patients were found to have no statistically significant difference in BNP concentrations between visits during follow-up (p=0.447), which leads to the severity of HF and confirms the positive effect of the optimised treatment scheme on prognosis and HF development in groups 1b and 2b.

In group 2b, were found significant differences in BNP concentrations at different patient visits (p=0.037). The level of BNP at the third visit was statistically significantly lower than at the first (p=0.009) and second visit (p=0.004). Aldosterone activates fibroblasts and stimulates the synthesis of type I and type III collagen by activating mineralocorticoid receptors (MCR), which contributes to the development of contractile dysfunction. Direct stimulation of cardiomyocyte receptors by aldosterone leads to myocardial hypertrophy and fibrosis. At the same time, blockade of MCR is accompanied by a decrease in left ventricular myocardial mass, an improvement in contractile function, and a parallel decrease in BNP, which is directly associated with clinical symptom and effects on HF progression.

Table 2

Dynamics of natriuretic peptide concentration in the blood of patients with acute myocardial infarction comorbid with type 2 diabetes mellitus during treatment, pg/mL

Visit	Group	
	Group 1a	Group 1b
First	428.54±17.76^	419.13±12.79**^^
Second	437.28±13.52*^	401.73±15.20**^^
Third	413.45±20.06*^	277.84±15.13

Note: * – p<0.05 compared with the optimised scheme, ** – p<0.05-compared with the third visit, ^ – p<0.05 compared with group 1a, ^^ – p<0.05- compared with group 1b

Group 2b patients had lower BNP levels at the second (p=0.042) and third (p=0.003) visits compared with group 2a. This was associated with the absence of specific factors influencing MCR blockade and the development of pathological remodelling in group 2a, which in turn influenced HF, both in the acute myocardial infarction and postinfarction period.

Analyzing data from subgroups which received the optimised treatment scheme, we observed no statistically significant difference in BNP blood concentrations between group 1b and 2b patients (p=0.384). The high efficacy of eplerenone in postinfarction remodelling of left ventricular myocardium proves that its use is also reasonable in patients with DM2, as it reduces mitochondrial oxidation and apoptosis in cardiomyocytes in DM2 without the influence of glycaemia. It is important to note that AMCP has no effect on blood insulin levels and fasting glycaemia. This proves the neutral metabolic profile of eplerenone. Interestingly, the decrease in BNP concentration at the third visit in groups 1b and 2b below the critical level for the diagnosis of CH, of 300 pg/mL, indicates the efficacy of the treatment. BNP has a high prognostic value in the diagnosis of HF and has therefore been used as a biological marker of LV dysfunction.

Early prescribing of AMCP has been proven safe and effective in reducing BNP, a marker of HF and adverse outcomes, in both the acute and post-infarction periods and can prevent the onset of HF symptoms in post-AMI patients with and without concomitant DM2.

Comparing the baseline data of all 4 subgroups at the first visit, it was found that group 2a had a significantly higher BNP concentration than group 1a (p=0.008) and 1b (p=0.011), while group 2b also had a higher BNP concentration than group 1a (p=0.013) and group 1b (p=0.018), a statistically significant level. The differences between patients with and without concomitant DM2 suggest that the severity of HF increases in the presence of comorbid endocrine pathology. Thus, patients with AMI and HF and concomitant DM2 need glycosylated haemoglobin (HbA1c) monitoring for prognostic assessment of the course of the major disease.

The data analysis on HbA1c in patients' blood showed statistically significantly lower levels in group 1 compared to group 2. A significant difference was detected: in group 1a – 5.1±0.1 %, 1b – 5.5±0.4 %, and in group 2a – 7.1±0.2 %, 2b – 7.7±0.6 % (p<0.001), which confirms the presence of DM2 in group 2 patients and argues for the negative impact of carbohydrate metabolism disorders on development and severity of HF course. It can therefore be assumed that hyperglycaemia preceded the development of AMI.

Dynamics of HbA1c concentration in blood of patients with AMI and concomitant DM2 at the second visit of group 2a was 6.9±0.3 %, at the third visit – 6.7±0.2 %, and group 2b at the second visit – 6.8±0.4 %, at the third – 6.6±0.3 %. Analysing data from subgroups receiving the optimised treatment scheme, we observed no statistically significant difference in blood HbA1c concentrations between Group 2a and Group 2b patients at the first visit (p=0.384), second visit (p=0.674) and third visit (p=0.724), indicating a general course of comorbid diabetes mellitus.

During correlation analysis on the first visit, a direct strong correlation between BNP and HbA1c parameters was found (r=0.713, p=0.009), which indicates the unity of HF development in AMI patients with concomitant DM2 and creates the preconditions for consideration of the interaction of these laboratory parameters in the models of prognosis course of AMI complicated by HF.

A comparative analysis of BNP concentration at the third visit between the groups showed that it was significantly higher in group 2a than in group 1a, i.e. the dynamics of HF reduction during protocol treatment were worse in the group with AMI and HF and comorbid DM2. However, no statistically significant difference was found between groups 1b and 2b (p=0.238), and level concentrations of BNP were below the threshold for confirmation of HF. Therefore, the effectiveness of eplerenone in patients with comorbid DM2, as well as in patients with AMI and HF without concomitant carbohydrate metabolism, has been shown to be similar.

Assessment of baseline BNP concentrations revealed that the combination of DM2 with AMI significantly contributed 23 % (p<0.05) to the negative impact of metabolic disturbances on prognosis and course severity of HF. The data analysis of second and third visits in groups 1 and 2 confirm the conclusions that the use of eplerenone leads to a decrease in blood serum level of BNP, which prevents the progression

of HF, affects its severity, increases tolerance to physical activity, reduces symptoms and improves the quality of life in these comorbid patients.

Currently, the search for and highlighting of haemodynamic parameters of predictive value for HF and the development of prognostic models for the course of HF in AMI patients, especially in patients with concomitant DM2, is still an open question [12,13].

The development of HF also depends on LV remodelling, a process characterised by progressive ventricular dilatation followed by impaired systolic function with decreased EF [11, 12]. The clinical symptoms of HF are also a consequence of cardiac remodelling, which involves damage to cardiac and extracellular matrix cells with subsequent cell hypertrophy, myocyte apoptosis and necrosis, fibroblast activation and proliferation, ultimately leading to widespread fibrosis and dysfunction [7, 11].

Therefore, it stands to reason that pathogenetic therapy in patients with and without DM2 is the use of AMKR [8] not only after an AMI but also in the acute period.

Accordingly, an optimised treatment scheme in combination with eplerenone at a dose of 25 mg/day can not only improve the quality of life in AMI patients with and without concomitant DM2 but also affect the prognosis and course of HF.

Conclusion

The work presents a theoretical synthesis and solution of a topical problem of modern internal medicine, specifically increasing the effectiveness of diagnosis and treatment of heart failure by creating a new scientific concept based on optimization of treatment of patients with acute myocardial infarction in combination with and without type 2 diabetes mellitus by combining standard therapy with a mineralocorticoid receptor antagonist – eplerenone, and using natriuretic peptide as a marker of cardiac insufficiency development.

Additional prescription of standard therapy with eplerenone to patients with acute myocardial infarction in combination with and without type 2 diabetes has a positive effect on treatment effectiveness and the course of heart failure, which is confirmed by a decrease in natriuretic peptide levels ($p<0.05$), one of the leading indicators of treatment effectiveness and progression of heart failure.

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