EFFECTS OF ADDING NICORANDIL TO STANDARD THERAPY IN PATIENTS WITH ISCHEMIC HEART FAILURE

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Abstract: *Introduction. Nicorandil, a vasodilator with strong coronary and peripheral vascular activity is current used as an antianginal agent, but its effect in heart failure (HF) patients has not been fully established. Therefore, we examined impact of nicorandil in outcomes of ischemic HF patients. Materials and methods. HF patients with ischemic etiology were prospectively registered and divided into 2 groups based on oral administration of nicorandil: nicorandil group (n = 6) and non-nicorandil group (n=6). Patients were randomly assigned to be treated with or without oral nicorandil, 10 mg twice daily for 5 days. BNP values were measured at admission and at 5th day. Patients undergo ecocardiography exam and 6 minutes walk test. Results: Echocardiographic measurements showed no statistical relevant differences between groups. The mean distance at the 6minute walk test has higher in the nicorandil group (396 meters) versus non-nicorandil group (320 meters) and BNP levels after 5 days were decreased significant in the nicorandil group. Conclusion: Nicorandil is potentially effective for treatment in patients with ischemic heart failure.*

INTRODUCTION

Heart failure (HF) is a major public health problem in developed and developing countries, reaching epidemic proportions. About 1–2% of the adult population in developed countries suffer from HF, with a prevalence of more than 10% among the elderly (> 70 years).(1)

The number of cases of heart failure is constantly increasing due to the cumulative effect of aging of the population but also to improving the survival of patients with cardiovascular diseases due to the revascularization therapy of coronary heart disease.(2)

Nearly 70% of all IC syndromes can be attributed to underlying myocardial ischemia. Despite efforts to address the key risk factors for ischemic heart disease, the incidence of HF hospitalizations does not decrease, but in fact continues to increase.(3)

Ischemia plays an essential role in the development and evolution of heart failure. Tissue loss following a myocardial infarction and chronic ischemia are trigger factors for ventricular remodeling and heart failure development.(4)

Vasodilators are used in conventional treatment for urgent care of patients with heart failure.

Clinical recommendations for the diagnosis and treatment of acute and chronic heart failure translate the complexity of scientific research findings into recommendations for daily practice.(5)

Nicorandil, a nicotinamide derivative, developed as a vasodilator with strong coronary and peripheral vascular activity is used as an antianginal agent. It has a nitrate component and an ATP-sensitive K-channel opener.

Nicorandil, thus, has a dual mechanism of vasodilation, which increases coronary blood flow, reduces preload and afterload and has been shown to have similar antianginal effect with other traditional drugs.(6)

In addition, experimental studies have shown that nicorandil exerted cardioprotective effects by opening ATP-dependent mitochondrial potassium channels and reducing oxidative stress. On the other hand, by opening the ATP-dependent potassium channels, cardioprotective effects may occur by reducing excitability, so that calcium overload and energy consumption would be alleviated.(7)

Cumulative evidence suggests that nicorandil has several beneficial effects on the myocardium and may play an important role in heart failure therapy.

AIM

The aim of the present study was to assess the efficacy of therapy with nicorandil in hospitalized with ischemic chronic heart failure.

MATERIALS AND METHODS

The current study is carried out prospectively, on a batch of 12 patients diagnosed with heart failure, admitted to the Cardiology Clinic of the Sibiu Clinical County Emergency Hospital in August-October 2016.

The study was approved by the ethics committee of the Hospital, and all patients provided written informed consent.

Inclusion criteria were: NYHA Class II-III, ischemic etiology at angiography, sinus rhythm, systolic dysfunction;

12 HF patients with ischemic etiology were prospectively registered and divided into 2 groups based on oral administration of nicorandil: nicorandil group (n = 6) and non-nicorandil group (n=6).

All patients also received standard treatment for HF (betablockers, mineralocorticoids, diuretics and angiotensin-converting enzyme inhibitors). Patients were randomly assigned to be treated with or without oral nicorandil, 10 mg twice daily for 5 days. Each patient undergoes ecocardiography and a-6-minute walk test.

Echocardiography scans were performed by one experienced physician sonographer using Siemens Acuson C70 ultrasound scanner. Left ventricular (LV) ejection fraction (EF)

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were measured (Simpson's biplane method), mitral annular plane systolic excursion (MAPSE): measured in M mode in the apical 4 chambers, diastolic function was assessed using E/e' slope.

BNP values were measured at admission and at 5th day. We assessed BNP levels, the number of days of hospitalization for each group.

RESULTS

66,6% of the patients were men, mean age was 67 years, without differences between groups and mean length of inpatient stay was 7.8 days.

Table no. 1. Clinical and echocardiographic features

	Nicorandil group	Non-nicorandil group	p
Age (years)	63.83±4.19	69.67±5.2	0.427
Sex (male)	66.6%	66.6%	1
Hypertension	5 (83.3%)	4 (66.6%)	
Diabets melltius	3 (50%)	1 (16.6%)	
Chronic renal disease	1 (16.6%)	3 (50%)	
LVEF %	39.33±15.17	39.83±14.75	0,955
MAPSE (mm)	11.20±2.55	12.08±5.12	0,378
Δp/Δt	585.75±270.83	402.66±40.06	0,308
E/e'	8.13±0.77	6.62±2.24	0,177

Patients were followed for 16 months to determine the need for rehospitalization /death (event) and to assess the length of free event period.

Hypertension was the most important risk factor; it was present in 75% of the patients.

Diabetes mellitus was present in 50% of patients from nicorandil group, and 16,6% of the non-nicorandil group.

Echocardiographic measurements showed no statistical relevant differences between groups. LVEF was reduced in both groups (39%), MAPSE was slightly higher in non-nicorandil patients and Δp/Δt was better in nicoradil group.

Table no. 2. Clinical and paraclinical assessment

	Nicorandil group	Non-nicorandil group	p
BNP (pg/ml)	221	14	0.038
Length of hospitalization (days)	7.17±0.833	7.33±0.760	0.855
6MW distance (m)	396±87.1	320.83±118	0.234
Time to event (days)	183.33±83.92	172 ±87.81	0.928

BNP levels after 5 days decreased significantly in the nicorandil group versus non-nicoradil group.

Mean length of hospitalization was 7.2 days, without any difference in the two groups.

The mean distance at the 6-minute walk test has higher in the nicorandil group (396 meters) versus non-nicorandil group (320 meters).

Treatment with nicorandil did not affect time to next hospitalization due to worsening of heart failure.

DISCUSSIONS

The mean age of the subjects was 63 years, and most of the patients were males, without differences between the two groups and similar to dates from other studies.

The prevalence of comorbidities in patients in this study is comparable to studies in the literature that have investigated the impact of nicorandil treatment on ischemic cardiomyopathy. In our cohort, 75% of the patients were hypertensive, which was the most important risk factor present. Hypertension is an established independent risk factor for HF in all populations accounting for approximately 47% of ischemic events.(8)

Diabetes mellitus was present in half of the patients in the present study.

The function of the left ventricle in the study patients was characterized by several echocardiographic measurements. The most versatile ultrasound parameter used to define systolic dysfunction is the left ventricular ejection fraction, which is used in most studies. The mean FEVS in patients in our cohort was 39%.

MAPSE is an echocardiographic marker derived in the M mode of longitudinal function of the left ventricle. It has been suggested that MAPSE is a surrogate measurement for systolic function.(9) In this study, there were no significant differences between groups.

The Δp/Δt index derived from the continuous Doppler of the mitral regurgitation jet is a noninvasive parameter that characterizes the isovolumetric phase of the cardiac cycle being both a parameter of systolic function and diastolic function of the left ventricle.(10)

Prognostic values of BNP levels are well established as having an independent prognostic value. A meta-analysis on the importance of BNP use in heart failure showed that each increase of 100 pg/ml was associated with a 35% increase in the relative risk of death.

Most studies that analyzed the effect of nicorandil in heart failure patients used the natriuretic peptides (BNP and NT-pro BNP) as a humoral reference. In our study, the decrease of BNP level in nicorandil group was significantly greater than in the control group.

No significant differences were observed between the mean length of hospitalization of the two groups in our study.

The distance walked over 6 min is an alternative measure of function that has also been applied as the basis of cardiac function-based prognostic assessments.(11) It also highlights its distinctive value as a measure of routine activity that may be more clinically relevant than a bicycle- or treadmill-based maximal functional evaluation

The mean distance walked in 6 minutes by the patients in our study was 355 meters, higher in the nicorandil group (396 meters) compared to the control group (320 meters).

The present study proves that nicorandil therapy can improve the outcomes of patients with ischemic cardiomyopathy by improving the walking distance. Also use of nicorandil is decrease the level of BNP.

Limits

The most important limitation of the present study is the small number of patients included in the two groups.

Another limitation of the study was the use of nicorandil for a limited period of time. The outcomes of nicorandil treatment for a longer period would give better information in clinical improvement and prognosis of patients with heart failure.

Further studies are required**.**

CONCLUSIONS

The functional capacity expressed by the six-minute walk distance was higher in ischemic heart failure patients treated with nicorandil than those with conventional treatment.

The patients in the nicorandil group had higher decrease of BNP levels without shortening the length of hospitalization.

Time to exacerbation of symptoms with the need for hospital admssion was similar for the two groups.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139:e56-e528.
2. Ponikowski P, Voors A. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal; 2016. p. 2129-2200.
3. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S.1979 to 2004. J Am Coll Cardiol. 2008;52:428-434.
4. Cowie MR. Essentials of heart failure. Ed Wiley Blackwell; 2013. p. 1-9.
5. Elgendy I, Mahtta D, Pepine CJ. Medical Therapy for Heart Failure Caused by Ischemic Heart Disease. Circ Res. 2019 May 24;124(11):1520-1535.
6. Das B, Sarkar C. Cardiomyocyte mitochondrial KATP channels participate in the antiarrhythmic and antiinfarct effects of KATP activators during ischemia and reperfusion in an intact anesthetized rabbit model. Pol J Pharmacol. 2003;55:771-786.
7. Abdel-Raheem IT, Taye A, Abouzied MM. Cardioprotective effects of nicorandil, a mitochondrial potassium channel opener against doxorubicin-induced cardiotoxicity in rats. Basic Clin Pharmacol Toxicol. 2013;113:158-166.
8. Shrestha PL, Shrestha PA, Vivo RP. Epidemiology of comorbidities in patients with hypertension. Curr Opin Cardiol. 2016;31(4):376-80.
9. Hu K, Liu D, Herrmann S. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. Eur Heart J Cardiovasc Imaging. 2013;14:205-212.
10. Kolias T, Aaronson K, Armstrong W, Doppler-Derived dP/dt and2dP/dtPredict Survival in Congestive Heart Failure.JACC 2000;36:1594-9.
11. Du H, Newton PJ, Salamonson Y, et al. A review of the six-minute walk test: its implication as a self-administered assessment tool. Eur J Cardiovasc Nurs. 2009;8:2-8.