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LONG-TERM EFFECTS OF METOPROLOL AND IVABRADINE IN REPERFUSED ANTERIOR MYOCARDIAL INFARCTION: MET-IVA STUDY (*CLINICAL FINDINGS AFTER 8 YEARS OF FOLLOW-UP*)

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ABSTRACT

Background: Heart rate is a determinant of myocardial oxygen demand and in myocardial infarction it is related to mortality. Ivabradine is a pure cardiac agent that reduces speed and has no effect on blood pressure and contractility and can reverse left ventricular remodeling. B-blockers in ST-elevated myocardial infarction (STEMI) are indicated for patients without a contraindication, particularly in patients with high heart rate or blood pressure. Epidemiological studies have shown that the increase in CF represents a risk factor for cardiovascular morbidity.
Aim of the study: The aim of this work is to evaluate the effects of ivabradine versus metoprolol in reperfused anterior STEMI after 8 years of follow up, the our primary end point was to analyze the quality of life during the 8 years of follow up.
Methods: In this prospective study, comparison between baseline and follow-up IVA (ivabradine) and METO (metoprolol) data was performed for patients with successful PCI for anterior STEMI with an impaired left ventricular function and high HR and sinus rhythm.
The discharged reperfused anterior STEMI (PCI-Treated) patients were followed and they carried out periodical controls in our department to analyze the incidence of ischemic events and other problems and further the patients were undergone to questionnaire on quality of life (EQ-5D-5L). Clinical and echocardiographic data were also were analyzed.
Results: At baseline in the study group, HR was significantly reduced in both groups, the IVA group showed a significant increase in EF (51.92 +\- 5.94 vs 44.5 +\- 4.44, p<0,001), but all parameters remained unchanged after 8 years (ex: HR: 66.42 +\- 4.46 vs 66.09 +\- 4.50; p>0,743). Most of IVA group have reported a good quality of life related to health in comparison with metoprolol group. The EQ-VAS Score for IVA group is 1.3 points higher than the average EQ-VAS score for METO group.
Conclusions: This study shows not only that ivabradine improves LV remodelling after AMI when added to current guideline-based therapy, in STEMI patients treated with successful PCI, but shows mostly that the beneficial effects were continued during the subsequent 8 years, showing IVA group a significant reduction in LVEDV and LVESV indexes compared with the METO group after 8 years, as well as a better quality of life.

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INTRODUCTION

Acute myocardial infarction (AMI) induces scar formation and changes in the surviving myocardium, designated as post-AMI ventricular remodelling (Mitchell et al., 1992).

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Tachycardia is common in the acute stage of ST-elevation myocardial infarction (STEMI), whether related to the sympathetic nervous system activation caused by pain or as a compensatory phenomenon to acute heart failure complicating STEMI (Collins and Fox, 1990). It increases the imbalance between the oxygen supply to the area at risk (which is limited by occlusion of the infarct-related artery) and myocardial oxygen demand, in which it plays a critical role (Fox et al.,

2007). Adverse left ventricular (LV) remodel ling, defined as an increase in LV end-systolic volume (LVESV) is associated with progression to heart failure and poor outcome. The therapeutic effects of beta blockade, angiotensin-converting enzyme inhibition and mineralocorticoid receptor antagonist (MRA) inhibition have been linked to their beneficial effects on cardiac remodeling. Blockade of b-1 receptors results in slowing of heart rate (HR), reduction in myocardial contractility, and lowering of systemic blood pressure (BP). Furthermore, b-blockers may reduce the risk of ventricular arrhythmias, which are an important cause of death after STEMI. In STEMI patients treated with primary percutaneous intervention (PPCI), HR at discharge has been found to correlate with mortality. The results of the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) showed that an HR decrease with ivabradine reversed LV remodelling in patients with heart failure. Ivabradine is an If channel blocker, which produces pure heart rate reduction in patients in sinus rhythm. Ivabradine lowers HR without any negative inotropic or lusitropic effect, thus preserving ventricular contractility. Aim of the study was to evaluate the long term effects in patients receiving ivabradine in early phase (within 12 hours from PCI) in anterior reperfused STEMI and which continued ivabradine for the subsequent 8 years in comparison with patients receiving metoprolol in early phases (within 12 hours from PCI) (Fasullo et al., 2009).

MATERIALS AND METHODS

Population

Between January 2009 and December 2017, 104 patients with a first anterior STEMI reperfused with an ejection fraction < 50% and receiving metoprolol or Ivabradine, were evaluated and followed for 8 years through phone call and annual clinical control.

Eligibility Criteria

Patients had to have a first anterior episode of STEMI, Killip class I-II, an acceptable echocardiographic window. In addition, all patients could not show any rhythm and conduction disturbance and to be in sinus rhythm and with a mean HR> 80 beats/min. All patients were randomized (double blind) in 2 groups: a group received b -blockers (76 patients: METO group) 12 hours after successful PCI and the other group received ivabradine (79 patients: IVA group) 12 hours after successful PCI. The IVA and metoprolol groups continued the treatments orally (IVA 5 mg/twice a day) (Metoprolol 50 mg bid and few cases increased up to 100 mg bid in patients with HR > 70 beats/min and acceptable pressure values) [Table 1].

Table 1. Clinical data of the enrolled patients

	METO	IVA	*P*
Patients	38	42	NS
Sex F/M	17/21	20/22	NS
Age (y)	65.42+\-3.93	66.42 +\- 3.97	NS
Hypertension	36	36	NS
Diabetes	24	22	NS
ACE-i \ ARBs	30	32	NS
MRA	18	20	NS
ASA\clopidogrel	38	42	NS
Statins	35	39	NS

Patients underwent echocardiographic evaluation by two-dimensional (2D) ultrasound periodically (every 12 months). Futher ,all patients were controlled in cases of new events or news symptoms.

Exclusion Criteria

Patients not suitable for immediate PCI or with time from onset symptoms >4 hours and with positive TNI, with left bundle branch block, a history of cardiomyopathy, or heart failure, previous STEMI, PCI, coronary artery bypass grafting, and patients with b-blockers intolerance or contraindications, and those who received reperfusive pharmacological treatment (thrombolysis) (Fasullo et al., 2009).

Statistical Analysis

Results are expressed as mean SD. Data were analyzed using the 2-tailed test to identify differences between groups. Nominal data was analyzed by the chi-square test; $P < 0.05$ was assumed as statistically significant.

RESULTS

Hospital readmissions, side effects, atrial fibrillation episodes, and cardiac mortality were analyzed. [Table 2]. Furthermore blood pressure (BP), heart rate (HR) and echocardiography data (ESV, EDV, EF) were measured. From a total of 104 patients, 6 were lost in follow-up (3 IVA group and 3 METO group).There were 16 deaths (8 IVA group and 8 METO group). The dose of ivabradine was 5 mg bid in 38 patients and 7.5 mg in 4 patients only. Metoprolol dose was 100 mg bid in 30 patients, 50 mg bid in 4 patients, and 25 mg bid in 4 patients. Episodes of atrial fibrillation were more in the IVA group than in the METO group (8 vs 5). The frequent side effects in the IVA group were phosphenes (2 cases) and episodes of atrial fibrillation. However, 10 episodes of symptomatic hypotension and asthma (or bronchitis exacerbation) have been reported in the METO group. All treated patients showed a significant decrease of HR in comparison to its mean basal value. Systolic blood pressure did significantly change. In addition in all-IVA patients, left ventricular diastolic volume and left ventricular systolic volume significantly reduced. These changes of LV volumes caused significant increase of EF% [Table 3]. Quality of life was analyzed by administering a specific questionnaire (EQ-5D-5L) that gave a better feeling of health. The 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EQ-VAS Score in IVA group was: 85. This is 1.3 points higher than the average EQ-VAS score of 83.7 for METO group.

Table 2. Clinical Findings after 8 years of treatment

	Metoprolol (METO)	Ivabradine (IVA)	*P value*
Patients	38	42	NS
Readmissions (ischemic events and heart failure)	8	5	0,4328
Side effects	10	10	NS
EF %	44.5 +\- 4.44	51.92 +\- 5.94	0,001
LVEDV (ml\m2)	87.28 +\-5.33	81.59 +\-1.67	0,001
LVESV (ml\m2)	47 +\-2.81	44.69 +\- 1.99	0,001
HR (beats\min)	66.42 +\- 4.46	66.09 +\- 4.50	0,743
SBP (mmHg)	108.02 +\- 11.78	115.83 +\- 10.68	0,0028
Atrial fibrillation (parox-)	5	8	0,4328
Switch METO-IVA and IVA-METO	10	10	NS
Device ICD	1	1	NS
Combo Therapy (IVA-BB)	24	23	NS
Lost in Follow-up	3	3	NS
Mortality	8	8	NS

Note: the two-tailed P value is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant

Table 3. Comparison of clinical features after 60 days and 8 years

	60 days	*p60 days*	1 year	4 year	8 year	*P8 years*
IVA-Patients	77		71	65	42	
METO-Patients	74		68	62	38	
EDV - IVA	84.8+\-13	48	x	x	81.59 +\-1.67	0,001
EDV- METO	90.7+\-14	0,879	x	x	87.28 +\-5.33	0,001
EF - IVA	51.2 +\-9	0,001	x	x	51.92 +\- 5.94	0,001
EF - METO	47.2 +\-8	0,001	x	x	44.5 +\- 4.44	0,001
HR - IVA	66+\-7	NS	x	x	66.09 +\- 4.50	0,743
HR - METO	65+\-6	NS	x	x	66.42 +\- 4.46	0,743
LIFE QUALITY - IVA	Good		Good	x	Good	
LIFE QUALITY - METO	Acceptable		Acceptable	x	Acceptable	

DISCUSSION

The results of the previous study are confirmed. Important has proved to be the tolerability and safety in patients with anterior STEMI with impaired ventricular function. The ivabradine group showed a significant reduction in ESV and EDV compared with the metoprolol group after 8 years (p 0.001) and a significant increase in EF in comparison with the metoprolol group (p.0.001). Both ivabradine and metoprolol are determined a significant and similar reduction in human resources. In contrast, the metoprolol group resulted in a more consistent reduction in SBP and DBP in comparison with the ivabradine group. Ivabradine (IVA) is effective in patients with coronary artery disease (CAD) or systolic heart failure in sinus rhythm. Its action consists in reducing heart rate (HR) and improving the time of left ventricular (LV) diastolic filling. Ivabradine lowers HR without any negative inotropic or lusitropic effect, thus preserving ventricular contractility. HR lowering with ivabradine dose-dependently increased diastolic time and reduced myocardial oxygen consumption.

The aim of this study was to evaluate the effects of IVA added to conventional therapy on patients with successful PCI for anterior STEMI with an impaired left ventricular function and high HR and sinus rhythm. After the addition of IVA to conventional treatment, HR significantly decreased in comparison to the baseline values. On the contrary, the echocardiographic indexes of LV diastolic dysfunction improved. Both IVA and METO have favorable effects on the myocardium, e.g., they enhance exercise tolerance and inhibit ischemia [Lance et al., 2009]. However, several studies, including the present study, have documented advantages of IVA over METO. First, IVA does not have negative inotropic or lusitropic effects; thus contractility is not impaired. Second, Iva facilitated more favorable remodeling. Thus, IVA has effects beyond HRR.

Limitation of the study

Although the study clearly demonstrated that IVA can bring important Doppler-echocardiographic and clinical advantages to CAD patients, it suffers from some limitations due to the little number of participants that could influence the results obtained and their statistical significance. A Despite these limitations, results obtained demonstrate that:

- IVA added to conventional therapy, can improve the main hemodynamics in CAD patients
- Doppler echocardiography is a useful and extremely sensitive tool to evaluate the usefulness of IVA in inducing
- This hemodynamic improvement.

Conclusion

These results testify that the addition of IVA to conventional therapy in patients with successful PCI for anterior STEMI with an impaired left ventricular function and high HR and sinus rhythm, can improve LV diastolic function evaluated by 2D and tissue Doppler-echocardiographic patterns. These Doppler-echocardiographic results match with the clinical improvement of patients evaluated. Our results suggest that ivabradine may be administered and continued in these patients. The signal of reduced left ventricular end systolic and end-diastolic volumes stay should be interpreted conservatively given the limited study size. This study shows not only that ivabradine improves LV when added to current

guideline-based therapy, in STEMI patients treated with successful PCI, but shows mostly that the beneficial effects were continued during the subsequent 8 years, showing IVA group a significant reduction in LVEDV and LVESV indexes compared with the METO group after 8 years, as well as a better quality of life. A larger sample of patients and further studies are required to evaluate the effects of ivabradine on clinical end points.

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