The Efficacy of Oral Ivabradine in Acute Phase in Non ST-segment Elevation Myocardial Infarction (NSTEMI) Post PCI: A Pilot Study

Manar M. Ahmed  
*National Heart Institute, Giza, Egypt*

Maggie M. Abbassi  
*Department of Clinical Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt*

Gamal Shaaban  
*National Heart Institute, Giza, Egypt*

See next page for additional authors

Follow this and additional works at: https://www.bfopcu.eg.net/journal

**Recommended Citation**
Available at: https://doi.org/10.54634/2090-9101.1024 https://www.bfopcu.eg.net/journal/vol59/iss1/5

The CLINICAL PHARMACY - ORIGINAL ARTICLE is brought to you for free and open access by Bulletin of the Faculty of Pharmacy Cairo University. It has been accepted for inclusion in Bulletin of Faculty of Pharmacy Cairo University by an authorized editor of Bulletin of the Faculty of Pharmacy Cairo University.
The Efficacy of Oral Ivabradine in Acute Phase in Non ST-segment Elevation Myocardial Infarction (NSTEMI) Post PCI: A Pilot Study

Authors
Manar M. Ahmed, Maggie M. Abbassi, Gamal Shaaban, and Samar F. Farid

This clinical pharmacy - original article is available in Bulletin of Faculty of Pharmacy Cairo University:
https://www.bfopcu.eg.net/journal/vol59/iss1/5
The Efficacy of Oral Ivabradine in Acute Phase in Non ST-segment Elevation Myocardial Infarction (NSTEMI) Post PCI: A Pilot Study

Manar M. Ahmed, Maggie M. Abbassi, Gamal Shaaban, Samar F. Farid

Abstract

Background: An elevated heart rate is a major risk factor for cardiovascular mortality and morbidity. This study aims to evaluate the beneficial effect of heart rate reduction of oral ivabradine in patients presenting with non ST-segment elevation myocardial infarction (NSTEMI) during acute stage post percutaneous coronary intervention.

Results: A total of 100 patients admitted to the emergency department, National Heart Institute, Cairo, Egypt, were randomized into two groups as follows: Group A: 50 patients with NSTEMI treated with ivabradine (5 mg twice daily) in addition to the conventional treatment; Group B: 50 patients with NSTEMI treated with the conventional treatment only. Demographic data, detailed history, clinical examination, chest pain onset, blood pressure, heart rate (HR), temperature and respiratory rate, electrocardiogram (ECG) as well as echocardiography and laboratory investigations were recorded. Patients were monitored for a period of 3–5 days (acute stage).

There was a significant difference between both groups regarding reduction of heart rate on discharge in patients presenting with NSTEMI (P < 0.05). However, there was no significant differences in mortality, heart failure (HF), cardiogenic shock, arrhythmia and any mechanical complications in the acute stage.

Conclusion: Ivabradine significantly reduced heart rate in patients with NSTEMI without affecting blood pressure or hemodynamics; however, this did not show a significant impact on major adverse cardiac events (MACE) during short-term follow up in the Coronary Care Unit (CCU) (Clinicaltrials.gov NCT04285736).

Keywords: Ivabradine, Non-ST elevated myocardial infarction, Heart rate, Major adverse cardiac events

1. Introduction

Ivabradine is an agent that acts by suppressing the heart rate and is used for symptomatic relief. Ivabradine acts by inhibiting the IF channel. This is the funny current or pacemaker current channels in the sinoatrial (SA) node; F is for “funny” so called due to its unusual properties compared with other current systems. Ivabradine is free from other cardiovascular adverse effects such as negative inotropy and increased intratrial, atrioventricular, and intraventricular conduction. Unlike β blockers, ivabradine has no effect on vascular demand [1–4] However, it has a favorable influence on stroke volume and myocardial oxygen rate-reduction. Also, it does not affect cardiac output, has no influence on stroke volume and blood pressure, either at rest or during exercise. [1,3–5].

Ivabradine was approved by the European Medicines Agency (EMA) in 2005 [1]. It is used for the symptomatic treatment of stable angina pectoris in patients with normal sinus rhythm. It is used for those who have a contraindication or cannot tolerate β blockers. It has been shown to be non-inferior to...
the β blocker atenolol for this indication and amlo-
dipine apart from angina. It is also being used off-
label in the treatment of inappropriate sinus tachy-
cardia [3]. It has been recommended in the 2016
ACC/AHA (American College of Cardiology/Amer-
ican Heart Association) guidelines for the manage-
ment of heart failure to reduce HF hospitalization for
patients with symptomatic (NYHA class II-III) stable
chronic heart failure with reduced ejection fraction
(HFrEF) (LVEF ≤35%) who are receiving GDEM
(Guideline — Directed Evaluation and Manage-
ment), including a β blocker at maximum tolerated
dose, and who are in sinus rhythm with a heart rate
of 70 bpm or greater at rest [4,6—9].

Heart rate reduction is beneficial for ischemic cardiovascular events, so its reduction may improve atherosclerosis, decrease myocardial oxygen de-
mand, decrease risk of plaque rupture and by pro-
longing diastolic time and enabling coronary
vasodilation, it increases myocardial oxygen supply
as well [1,3,4]. Also, heart rate reduction may reduce cardiovascular mortality and morbidity [10]. How-
ever, there are no sufficient studies in NSTEMI pa-
tients regarding the effect of heart rate reduction by
ivabradine post PCI.

Therefore, our aim is to study the heart rate reduction effect of oral ivabradine in patients pre-
senting with non-ST-segment elevation myocardial
infarction (NSTEMI) during acute stage following percutaneous coronary intervention (PCI).

2. Materials and methods

2.1. Study design

This was an interventional randomized parallel study.

This study was performed in the National Heart Institute (NHI), (Cairo, Egypt), from December 2014
till May 2016 on 100 patients admitted to theentechnology department of NHI with acute NSTEMI.
An informed consent was signed by all patients
upon admission after reading and clarification of the
aim and any potential hazard of the study. The
study protocol was approved by the Research Ethics
Committee, Faculty of Pharmacy, Cairo University.

Approval number CL (1200). This study was per-
formed according to the Declaration of Helsinki [11].

2.2. Patients

A total of 100 patients were recruited according to
the following criteria: Patients with NSTEMI with
normal sinus rhythm and heart rate (HR) more than
70 beats per minute (bpm) and systolic blood
pressure (SBP) > 90 mm Hg undergoing PCI were
included. The patients were excluded if they needed
urgent cardiac surgery, IV inotropic agents or had a
HR less than 60 bpm without any medication. Pa-
tients with liver impairment and decompensated
heart failure were not admitted to the department
where the study was performed and thus were
automatically excluded.

The patients were randomized by randomly
assigning each patient a number from 1 to 100 and
dividing into odd and even numbers. Fifty patients
with even numbers received ivabradine and fifty
patients with odd numbers did not receive ivabra-
dine. The intervention group (Group A) was treated
with ivabradine (5 mg twice daily) before PCI once
the patient was admitted in addition to the con-
tventional treatment. The control group (Group B)
was treated with the conventional treatment only.

All Patients received the following conventional
anti-ischemic measures according to guidelines:
aspirin 150 mg once daily after meal, clopidogrel
75 mg once daily, atorvastatin 40 mg once after
dinner. ACEI: captopril 25 mg adjusted according to
blood pressure, β blocker: cardio-selective bisoprolol
5 mg dose adjusted according to blood pressure and
heart rate and parenteral anticoagulant: enoxaparin
1 mg/kg twice daily, unless contraindicated and
adjusted when necessary. Oral ranitidine was given
as 150 mg twice daily or IV ranitidine three times a
day and diluted with normal saline.Any additional
medications needed for patient co-morbidities were
administered, with ensuring that no drug-inter-
actions occurred. Patients were monitored for a
period of 3—5 days during their stay in the CCU unit
(acute stage) for the following outcomes:

- Primary outcome: heart rate reduction, mortal-
ity, heart failure (HF, defined as EF<40%),
cardiogenic shock, arrhythmia, any mechanical
complication diagnosed by echocardiography
(acute mitral regurgite, ventricular septal rupture,
ventricular wall rupture ventricular aneurysm
and ventricular pseudoaneurysm).

- Secondary outcome: side effects of ivabradine.

The following baseline data were collected as well:
demographic data, detailed history and clinical ex-
amination, risk factors, medication history, any
possible drug interactions with ivabradine, onset of
chest pain, ejection fraction[EF] on admission,
 troponin (TnI), creatine kinase [CK], and its iso-
ensyme MB [CK-MB], serum creatinine, creatinine
clearance [CrCl], serum sodium, serum potassium,
echocardiography[ECHO], electrocardiogram
[ECG], alanine aminotransferase [ALT], aspartate
Table 1. Baseline demographic, clinical and laboratory data of patients. Data expressed as numbers (percentages) or mean ± standard deviation.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Group A (n = 50)</th>
<th>Group B (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n, %)</td>
<td>40, (80)</td>
<td>37, (74)</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.50 ± 7.75</td>
<td>60.88 ± 8.71</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.23 ± 3.45</td>
<td>21.64 ± 2.50</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Onset of chest pain before admission (hours)</td>
<td>9.62 ± 4.8</td>
<td>8.08 ± 4.94</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Heart rate on admission (beats per minute)</td>
<td>84.16 ± 10.090</td>
<td>81.74 ± 9.514</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.98 ± 6.45</td>
<td>36.68 ± 1.49</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Respiratory rate (number per minute)</td>
<td>18.70 ± 1.92</td>
<td>19.12 ± 2.01</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>EF on admission (%)</td>
<td>58.12 ± 9.94</td>
<td>56.12 ± 10.77</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Positive Troponin (n, %)</td>
<td>50 (100)</td>
<td>50 (100)</td>
<td></td>
</tr>
<tr>
<td>CK-MB (mcg/L)</td>
<td>65.48 ± 25.52</td>
<td>71.200 ± 30.95</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Total CK (mcg/L)</td>
<td>319.22 ± 167.49</td>
<td>714.64 ± 702.64</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.12 ± 0.32</td>
<td>0.95 ± 0.14</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>84.32 ± 7.26</td>
<td>85.18 ± 7.63</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>34.18 ± 10.71</td>
<td>38.12 ± 17.6</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>41.82 ± 14.07</td>
<td>44.20 ± 24.25</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>138.20 ± 5.44</td>
<td>133.90 ± 4.60</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.97 ± 0.44</td>
<td>3.95 ± 0.30</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>11.27 ± 1.92</td>
<td>12.05 ± 1.79</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>WBC (cells per cubic millimeter)</td>
<td>9930 ± 2.74</td>
<td>10 240 ± 2.70</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Platelets (cells per microliter)</td>
<td>244 580 ± 81.13</td>
<td>228 520 ± 33.56</td>
<td>P &gt; 0.05#</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>21, (42)</td>
<td>27, (54)</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Hypertension* (n, %)</td>
<td>30, (60)</td>
<td>25, (50)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)* (n, %)</td>
<td>18, (36)</td>
<td>26, (52)</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Previous IHD (n, %)</td>
<td>21, (42)</td>
<td>21, (42)</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Stroke (n, %)</td>
<td>3, (6)</td>
<td>3, (6)</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Family history of CAD (n, %)</td>
<td>17, (34)</td>
<td>10, (20)</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>18</td>
<td>26</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>0</td>
<td>3</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>4</td>
<td>4</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4</td>
<td>5</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>1</td>
<td>2</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td>1</td>
<td>3</td>
<td>P &gt; 0.05*</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5</td>
<td>5</td>
<td>P &gt; 0.05*</td>
</tr>
</tbody>
</table>

BMI, body mass index; HR, heart rate; EF, Ejection Fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; CK-MB, Creatine kinase-MB; CK, Creatine kinase; CrCl, Creatinine clearance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TLC, Total Leucocyte Count; IHD, ischemic heart disease; CAD, coronary artery disease. P < 0.05 = significant, P > 0.05 = non-significant. * Chi square test, # independent t-test.

*a Hypertension defined as blood pressure above 140/90 mmHg [12].

*b Diabetes mellitus defined as random plasma glucose ≥11.1 mmol/l (200 mg/dl) [13].

amino transferase [AST], white blood cell [WBC], red blood cell [RBC], hemoglobin [Hb] and platelet counts [PLT]. HR was measured every 2 h daily and ECG was done every 8 h daily. Echocardiography was done upon admission and discharge.

A checklist of ivabradine side effects was translated into Arabic (allergy, bradycardia, AV block, visual disturbance, headache, GIT disturbance, breathing difficulties, cold symptoms, confusion and depression) to check whether the patients suffered from any side effects. It was filled during discharge by the attending physician or the investigator.

2.3. Statistical analysis

Statistical analysis was performed using Statistical Packages of Social Science (SPSS 17.0) software. Continuous variables were expressed as mean ± standard deviation and compared using unpaired t-test. Categorical variables were reported as frequency (percentages) and compared by Chi square test. Paired t-test was used to compare between heart rate at admission and discharge in group A. Statistical significance was defined as P < 0.05.

3. Results

There were no significant differences between the two groups in demographic characteristics, baseline laboratory data as well as comorbidities, and medications administered upon admission (Table 1). The average stay in the CCU for patients in both groups was 4 days (range 3—5 days).
Table 2 compares HR on discharge, incidence of abnormal ECG, presence of depressed ST segment and inverted T wave in both groups. HR was significantly lower in the ivabradine group upon discharge. Ivabradine was associated with significant reduction of heart rate from admission to discharge as well (P < 0.05). For patients not taking ivabradine there was no significant difference from admission to discharge (P = 0.23). Tachycardia defined as heart rate greater than 100 beats per minute was noted in 3 patients in each group at baseline. At the end of the study only 1 patient in group 1 had tachycardia and 2 patients in group 2. (P = 0.56)

All patients were troponin positive with abnormal ECG on admission and discharge. Eighty percent showed ST depression on admission and 72% showed ST depression on discharge. Also, 58% showed inverted T wave on discharge. Comparison of cardiac adverse events showed an incidence of 4% with HF in each group, 2% arrhythmia, in group B, 4% cardiogenic shock in group A and 2% n group B, 6% mechanical complications, and 2% mortality rate (one patient in group A) during the study period with no significant difference between the two groups (Table 2).

Ivabradine side effects occurred in only 9 patients (18%). Two patients suffered from bradycardia (HR < 60 bpm), two complained of visual disturbances, two complained of breathing difficulties and one complained of headache.

4. Discussion

Ivabradine is studied extensively worldwide in clinical studies and the outcomes of these studies will define the real role of pure heart-rate control in cardiovascular medicine [3,4].

To the best of our knowledge this is the first study to evaluate the efficacy of oral ivabradine as an add-on to the background therapy in patients presenting with non ST-segment elevation myocardial infarction (NSTEMI) following percutaneous coronary intervention (PCI) during the acute stage.

There was a significant difference between both groups regarding reduction of heart rate on discharge in patients presenting with NSTEMI (P < 0.05), as well as significant reduction of heart rate from admission to discharge (P < 0.05). Heart rate reduction has become an essential therapeutic strategy as shown in international guidelines [14–16]. This may improve oxygen consumption and reduce myocardial perfusion time in the ischemic heart. Therefore, heart rate control decreases risk of adverse cardiac events, mortality, hospitalization for myocardial infarction, and heart failure [1,3]. It is also known that elevated heart rate is an important determinant of myocardial ischemia and is an established risk factor in cardiovascular disease [1,3].

When IV ivabradine was studied in the acute phase post PCI in STEMI patients (VIVIFY trial) (The eValuation of the IntraVenous If inhibitor ivabradine after ST-segment elevation mYocardial infarction trial) [17] heart rate was reduced over 8 h, with a faster and more marked decrease with ivabradine versus placebo. However, heart rate was similar in both groups after treatment discontinuation. There was no difference in cardiac biomarkers as well (creatine kinase (CK-MB), troponin T and troponin I). Even though left ventricular ejection fraction was similar in both groups, left ventricular end-diastolic volume and left ventricular end-systolic volume were lower in the ivabradine group.

The efficacy of ivabradine in two different populations was studied; BEAUTIFUL (morBidity-mortality EValuaTion of the If inhibitor ivabradine in
patients with coronary disease and left-ventricular dysfunction) [6,18] in 10917 patient for a period of 19 months and the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) [4] in 6505 patients with left ventricular ejection fraction of 35% or lower for 12–48 months. In the BEAUTIFUL trial [6,18], heart rate reduction was significant however, no significant reduction of the primary composite end point of cardiovascular death, admission to hospital for acute MI and admission to hospital for heart failure or cardiac death was reported overall. However, a subgroup analysis of patients in the same trial showed reduced risk [6]. In the SHIFT trial [4] ivabradine was shown to significantly reduce heart rate and major adverse cardiac events as well.

In our study, there was no significant statistical difference between both groups regarding the development of total major adverse cardiac events in the CCU. The possible explanation for this difference in results is differences in the underlying diseases in response to reduction of HR as this may reduce some adverse outcomes markedly in patients with CAD as in BEAUTIFUL or in patients with HF as in SHIFT trial more than in patients with NSTEMI. In addition, both trials studied a large number of patients for a minimum of 12 months whereas our study followed up a small number of NSTEMI patients in the acute stage only post PCI.

5. Conclusion

Ivabradine in addition to standard therapy, significantly reduces heart rate in patients with NSTEMI after PCI. However, this did not show a significant impact on major adverse cardiac events (MACE) during follow up from CCU admission to discharge. Therefore, ivabradine is recommended to be added to anti-ischemic measures in case of in case of ACS or when up titration of β-blocker is not possible.

Study limitations

Sample size was small as well as duration of the study was limited. Questionnaire was restricted to side effects upon discharge. Not all patients were capable of giving proper medication history prior to admission.

Acknowledgements

The authors acknowledge the National Heart Institute pharmacists, physicians and nurses for their support and help.

References

