University Heart Journal
Vol. 15, No. 1, January 2019

Comparison of the efficacy of Ivabradine and Nebivolol as Mono Therapy in the Treatment of Stable Angina Pectoris Patients with Mild Left Ventricular Dysfunction

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Abstract:

This prospective study aimed to investigate the efficacy of ivabradine and nebivolol in treatment of stable angina pectoris (SAP) patients with mild left ventricular dysfunction. Heart rate decreased (78±6) to (65±5) in Group: A and (77± 7) to (70 ± 5) in Group: B. There was no change in Blood pressure reduction in Group:A but significant BP reduction in Nebivolol group. Chest pain was reduced by Ivabradine but in Group : B, chest pain decreased in long term after 6 weeks time. After 6 months' treatment LVEF for the 15 patients of nebivolol group (50%; Group: A) improved by (48 ± 6.5) to (51 ± 3.2), (p>0.05) and for the 15 patients of Ivabradine group (50%; Group: B) (47 ± 5.4) to (51 ± 2.3), (p>0.05). Ivabradine can be considered as first choice in patient with tachycardia induced angina as this agent for reducing heart rate as well as chest pain. The hypertensive patient with tachycardia may be treated by Nebivolol. Among patients in which effective treatment could not be achieved at maximum nebivolol doses, more effective results were obtained in this study with Ivabradine.

University Heart Journal 2019; 15(1): 8-11

Introduction:

Atherosclerotic coronary artery disease is a chronic disease. Acute coronary syndrome can trigger patient mortality. Recently coronary artery disease mortality has decreased significantly in many European countries. About >80% of all coronary artery disease (CAD) deaths occur in developing countries. SAP is a clinical condition that is frequently encountered with CAD. New investigations are being developed for the diagnosis and prognosis of patients with SAP. It has been shown that mortality in chronic heart failure (CHF) patients may increase in relation to an elevated heart rate. With regards to CHF mortality, it has been observed that an increase in heart rate of 1 beat per minute increases the mortality risk by 3%, while an increase in heart rate of 5 beats per minute increases the mortality risk by 16%.[1,2] Ivabradine inhibits the pacemaker If current by slowing the diastolic depolarization slope in sinoatrial node cells in a dose-dependent fashion. When the available data regarding ivabradine is examined, it can be seen that ivabradine has the potential to slow-down the development of aterosclerosis, correct ischemia, and reduce the frequency of angina attacks, the prevalence of fatal and non-fatal myocardial infarction, and the rate patient hospitalization due to the said conditions.[1,2,3] The results of the BEAUTIFUL study[3] have demonstrated that ivabradine is a good choice for antianginal and antiischemic treatment, that it reduced the incidence of myocardial infarction and the need for coronary revascularization, and that it has a good tolerability profile when used in combination with other drugs. This study has also shown that ivabradine use represents an advancement in the treatment of stable angina pectoris patients with heart rates ≥70 beats per minute, and that the isolated decrease in heart rate caused by ivabradine decreased the occurrence of coronary events even in patients already receiving optimal cardiovascular protective therapies. The efficacy of beta-blockers in treatment coronary artery disease and stable angina pectoris patients is established in the current guidelines.[4,5] Among the different betablockers, nebivolol is a cardioselective agent that has long-term efficacy. To the best of our knowledge, our study is the first to comparatively evaluate mono- and combination therapies

Received: 5 November, 2018 **Accepted:** 15 December, 2018

of nebivolol and ivabradine as well as the early and six month late period efficacy of these drugs in stable angina pectoris patients with left ventricular ejection fractions (LVEFs) ≤40%.

Materials and Methods:

The study was approved by the local ethics committee. A total of 30 stable angina pectoris patients under follow-up in the cardiology department of Bangabandhu Sheikh Mujib Medical University (BSMMU) with LVEFs 45% to 50% were included into the study. The patient distribution according to gender was 21 male patients and 9 female patients (Table I). The age average was determined as 58±2. The patients were evaluated in 2 different groups (A, B). Only Nebivolol 5mg/day was administered to the 15 patients included in Group A. Fifteen patients who could not tolerate Nebivolol (due to COPD, bronchospasm, bronchial asthma, erectile dysfunction, insomnia, coronary vasoconstriction, hypotension) were started on Ivabradine 10mg/day and these patients were included into group B. The daily starting dose for Ivabradine and Nebivolol treatment was determined and administered by titration. The starting dose for Ivabradine was initially determined as 5 mg/day (administered twice daily), which was later increased to an average of 10 mg/day, and to a maximum dose of 15 mg/day for patients in which treatment effectiveness could not be achieved. The starting dose for Nebivolol treatment was initially 5 mg/day (administered one daily). According to the study criteria, patients with LVEF equal to 45% or below 50% were included into our study.

According to test reports, standard 12-Lead electrocardiographies (ECGs) were performed (all evaluated patients had sinus rhythm). Transthoracic echocardiography (ECHO) and ejection fraction were measured with the Simpson method (EF = left ventricle end diastolic diameter – left ventricle end systolic diameter/left ventricle end diastolic diameter x 100%). For the measurement of diastolic function, the following normal diastolic index parameters were taken as average references: E/A: 1.3 ± 0.4, IVRT: 63 ± 1.4 m/s, Deceleration time: 150-200 ms, P. vein Ar-A: 28 ± 6 ms, Em/Am: 2.1 ± 0.9. In addition to this, left ventricle diastolic dysfunction was staged as I, II, III or IV. Transthoracic echocardiography (ECHO) was performed with the GE vivid 7 machine. Statistical data were analyzed with SPSS programs.

Results:

Age is 58±2. Male and female ratio was 7:3.

The systolic and diastolic blood pressure values between the groups were measured as 145 ± 1.2 and 90 ± 2.5 for Group A, 145 ± 1.8 and 89 ± 2.2 for Group B at the beginning of study. The blood pressure values of patients with hypertension decreased to normal levels during and at the end of the treatment.

The average post-treatment systolic and diastolic blood pressure values between the groups were measured as 125 ± 2.1 and 82 ± 2.1 for Group A, 130 ± 2.4 and 85 ± 3.2 for Group B.

Heart rate decreased (78±6) to (65±5) in Group: A and (77± 7) to (70 ± 5) in Group: B. There was no change in Blood pressure reduction in Group:A but significant BP reduction in Nebivolol group. Chest pain was reduced by Ivabradine but in Group : B, chest pain decreased in long term after 6 weeks time. After 6 months' treatment LVEF for the 15 patients of Nebivolol group (50%; Group: A) improved by (48 ± 6.5) to (51 ± 3.2), ($p>0.05$) and for the 15 patients of Ivabradine group (50%; Group: B) (47 ± 5.4) to (51 ± 2.3), ($p>0.05$). There is no significant change in EF improvement in both groups.

These data include the pre-treatment initial results and the sixth month results.

A decrease in hospitalization was observed in each group.

According to these comparisons, an equal level of improvement in diastolic function was observed in the Group A nebivolol-using patients and the Group B ivabradine-using patients. Dose-related sinus bradycardia occurred in 1 (2%) of the nebivolol-using patients included in Group A. No medication or medication dose-related side effects or drug intolerances were observed in ivabradine-using patients included in Group B. The proteinuria and creatinine values were also assessed. No significant changes were observed in these parameters. Among patients treated with monotherapy by nebivolol and ivabradin, during treatment and at the end of the six month period, effects that concealed the symptoms of low blood sugar (fluttering, tachycardia) were observed in diabetic patients; however, these drugs did not have any negative effects on the lipid profiles. In contrast to nebivolol, erectile dysfunction was not observed among ivabradine-using patients. Nebivolol-induced bronchospasm, erectile dysfunction, asthenia, insomnia, coronary vasoconstriction, hypotension and/or allergic reaction to active molecule were observed in 15 patients with pre-existing COPD and bronchial asthma. These were not observed in ivabradine-using patients.

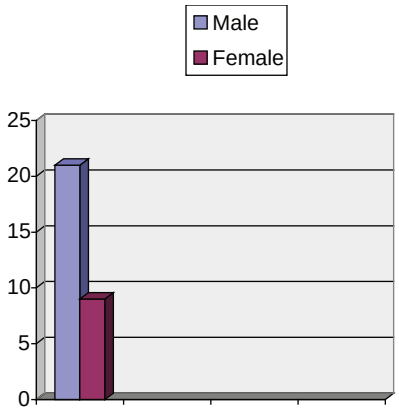

Fig.-1: *21 male and 9 Female patients of this study*

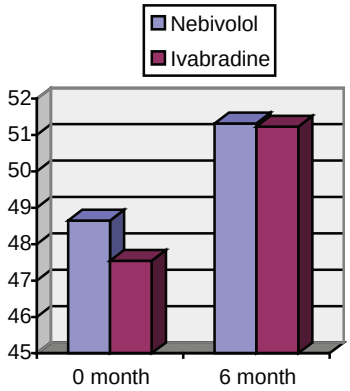

Fig.-2: *Improvement of EF in Group A (Nebivolol) and Group B (Ivabradine)*

Discussion:

In our study, we have compared the effects of ivabradine and nebivolol in stable angina pectoris patients with mild LV systolic dysfunction (LVEF ≤50%). No notable differences were observed in comparisons of nebivolol and ivabradine monotherapies' efficacy on the LVEF (nebivolol - LVEF 48 ± 6.5%; ivabradine - LVEF 47 ± 5.4). In the SHIFT [2] and BEAUTIFUL[3] studies, Ivabradine was reported as having no adverse effects on the LVEF. The results of the BEAUTIFUL study have demonstrated that ivabradine is a good choice for antianginal and antiischemic treatment, that it reduces the incidence of myocardial infarction and the need for coronary revascularization, and that it has a good tolerability profile when used in combination with other drugs. This study has also shown that ivabradine use represents advancement in the treatment of stable angina pectoris patients with heart rates of ≥70 beats per minute, and that the isolated decrease in heart rate caused by ivabradine decreased the occurrence of coronary events even in patients already receiving optimal cardiovascular protective therapies. In their efficacy study on ivabradine and nebivolol combination therapy performed with 92 patients, Tatarchenko et al. observed no difference between these two drugs with regards to antianginal, antiischemic and antitachycardia efficacy. [4] The results of this study are in parallel with the above mentioned studies. When ivabradine at a dose of 10 mg/day compared with nebivolol dose of 5 mg/day, we observed that the efficacy of both drugs further increased, while the daily dose requirement and the patients' use of nitrate and trimetazidine decreased. Even at minimal levels, the daily dose of the two preparations displayed efficacy equal to that of ivabradine and nebivolol in reducing the heart rate. In our study, the effects of the ivabradine and nebivolol mono therapies on the respiratory system were evaluated. According to our study's results, ivabradine has not demonstrated any effect that might lead to pulmonary dysfunction. It has been shown that ivabradine had no adverse effect on the pulmonary functions of patients with COPD and pulmonary hypertension in a study.[6] Our results have also demonstrated that ivabradine can potentially be used as an antitachycardia agent in patients with COPD, bronchospasm and bronchial asthma. We observed that nebivolol had minimal effect on pulmonary dysfunction. The effects of the ivabradine and nebivolol mono therapies on diastolic dysfunction were evaluated in our patients. During the pre-treatment and the six month treatment periods, ivabradine's efficacy on the diastolic parameters was found to be equal to that of nebivolol. De Luca et al have conducted on 111 patients with EFs below 50% described ivabradine's effect in improving diastolic parameters on its own. [7] Our results support the findings of the above mentioned study. To the best of our knowledge, our study is the first comparative study to be conducted in Bangladesh on ivabradine and nebivolol-using stable angina pectoris patients with a LVEF ≤50%. In our study, we have compared the rates of hospitalization observed with mono therapies of ivabradine and nebivolol in stable angina pectoris patients with LVEF 45 to 50%. Among patients included into Group A and B, no hospitalization was observed by the end of the six month. While no significant differences were noted between these two groups (Group A and B). However, as ivabradine and nebivolol tend to conceal the symptoms of low blood sugar (fluttering, tachycardia), they should be used cautiously in diabetic patients. We have determined that the frequency of side effects observed in ivabradine monotherapy (such as dose

intolerance-related bradycardia) as well as the frequency of side effects that may develop as a result of nebivolol monotherapy such as bronchial asthma, bronchospasm in COPD patients, erectile dysfunction, insomnia, hypotension, sinus bradycardia and headache decreased at minimal levels. These two drugs in monotherapy would provide a safer approach with regards to the side effect profile.

Conclusion:

Ivabradine can be considered as first choice in patient with tachycardia induced angina as this agent for reducing heart rate as well as chest pain. The hypertensive patient with tachycardia may be treated by Nebivolol. Among patients in which effective treatment could not be achieved at maximum nebivolol doses, more effective results were obtained in this study with Ivabradine.

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