TAJ June 2023; Volume 36 Number-1

ISSN 1019-8555
The Journal of
Teachers Association
RMC, Rajshahi

Original Article

# Comparison of Effect of Conventional Medical Management and Ivabradine with Conventional Medical Management on Quality of Life in Patients with Chronic Heart Failure

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## Abstract

**Background: The study aimed to see the effectiveness and role of ivabradine on the quality of life in chronic heart failure suffering patients. This open-label Randomized controlled Trial was conducted to assess the effect of ivabradine plus conventional medical management over conventional medical management on quality-of-life parameters among 100 patients of chronic heart failure from January 2021 to December 2021 in the Department of Pharmacology & Therapeutics in collaboration with the Department of Cardiology & Medicine, Rajshahi Medical College Hospital, Rajshahi.**

**Materials and methods: According to the drug allocation study population was divided into a control group (50 patients) and an experimental group (50 patients). Minnesota Living with Heart Failure questionnaire (MLWHFQ) was used to assess the quality of life, and the resting heart rate was measured by 12-lead electrocardiography. Baseline demographic and clinical characteristics were recorded, and patients were followed up at four weeks and 12 weeks of treatment.**

**Results: The comparison of mean differences of MLWHFQ score at first and second follow-up visits between the two study groups was statistically significant [t (100) = 2.43 p < 0.05 & t (100) = 6.60 p < 0.001 respectively]. According to the MLWHFQ cut-point score, it was also observed that poor baseline quality of life gradually shifted to good quality after four weeks and 12 weeks of treatment, and it was proportionately higher in the experimental group. Relations between the respondents of both study groups and their different qualities of life during the first follow-up visit ($\chi 2 = 13.69$, df = 2, $p < 0.05$) and second follow-up visit ($\chi 2 = 22.79$, df = 2, $p < 0.001$) were statistically significant.The comparison of the mean (±SD) heart rate between the two study groups was statistically significant (p <0.001) only during the second follow-up visit.**

**Conclusion: This study concluded that adding ivabradine to conventional medical management in treating patients with chronic heart failure improves their symptoms, quality of life, and heart rate and ultimately reduces the morbidity and mortality of such patients.**

**Keywords: Ivabradine, conventional medical management, quality of life, chronic heart failure.**

**TAJ 2023; 36: No-1: 01-08**

## Introduction

Heart failure (HF) is a common and disabling condition that significantly impacts health-related quality of life. Health-related quality of life refers to the subjective perception of health, i.e., the impact of disease and treatment on health status

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(symptoms, daily functioning, and subjective well-being). Therefore, HQoL evaluations are critical in a chronic, disabling condition, such as HF, because the primary goals of treatment include relief of symptoms, optimization of daily functions of life, and minimization of the impact of disease on well-being.[1] Elevated resting heart rate (HR) is an established marker of adverse cardiovascular outcomes in various patient populations.[2]

The sympathetic nervous system (SNS) activation clinically manifests as increased resting HR in chronic heart failure patients. Therefore, beta-blocker is one of the most important therapeutic strategies to suppress SNS in managing HF.

A substantial proportion of patients cannot tolerate target dosages of beta blockers due to their undesirable hemodynamic effects. It has been observed that only about 25% of HF patients actually receive the recommended target dose of beta-blocker.[3] Moreover, 10-15% of the patients never receive a beta blocker due to their co-morbidities, such as obstructive airway disease. So, the development of novel and complementary non-beta blocked therapeutic targets that can synergistically reduce HR is crucial to achieving better cardiac outcomes in HF. So, a therapeutic agent that solely affects heart rate is highly demanded. Ivabradine is a novel agent that significantly reduces heart rate without additional unwanted effects. Ivabradine inhibits the Ionic $I_f$ current (Funny Channels) that modulates the pacemaker activity of the SA Node, with no additional effects on other ionic channels or receptors in the heart or vascular system.

Ivabradine lowers heart rate by acting selectively and specifically on the cardiac pacemaker current ($I_f$) that controls the spontaneous diastolic depolarization in the sinoatrial (SA) node and hence regulates the heart rate. Ivabradine specifically affects the SA node, having no effect on blood pressure, intracardiac conduction, myocardial contractility, or ventricular repolarization.[4]

The discovery of $I_f$ current, which modulates the slope of spontaneous diastolic depolarization of the sinoatrial node, has led to a novel non-betablockade approach to HR reduction. HR reduction by Ivabradine improved Quality of life (QOL) in the INTENSIFY study and secondary analysis from the SHIFT trial. So, there was a clear relationship between the magnitude of HR reduction & improvement of QOL.[5]

The data on the efficacy of ivabradine as an add-on therapy are scarce in our Bangladeshi population. Therefore, the present study was conducted to assess the effect of Ivabradine plus conventional medical management over conventional medical management on quality-of-life parameters in patients with chronic heart failure that may help specialized physicians, cardiologists, and internists in treating CHF patients.

## Materials and Methods

This open-label randomized controlled Trial was conducted to assess the effect of Ivabradine plus conventional medical management over conventional medical management on quality-of-life parameters among 100 patients of chronic heart failure from January 2021 to December 2021 in the Department of Pharmacology & Therapeutics in collaboration with the Department of Cardiology & Medicine, Rajshahi Medical College Hospital, Rajshahi. Diagnosed patients with chronic heart failure due to dilated cardiomyopathy and ischemic heart disease with age $\geq$ 18 years were included in the study. All patients were on conventional medical therapy, including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, nitrates, and digoxin. Patients with NYHA class I HF, pregnant female, patients suffering from advanced liver failure and patients suffering from advanced renal failure were excluded from the study.

Demographic characteristics, like age, gender, body mass index (BMI), relevant medical history, risk factors, and concomitant medications, were recorded in the preformed data sheet. A baseline assessment of a symptomatic class of heart failure was done by using the NYHA classification. The Minnesota Living with Heart Failure questionnaire (MLWHF) was used to assess the quality of life

data, and resting HR was measured by 12-lead electrocardiography in the supine position. All patients had undergone some baseline investigation, including ECG, Echocardiography, Chest X-Ray, and Liver and Renal Functions test. The resting heart rate and quality of life parameters were re-assessed by follow-up after 1 and 3 months.

## Results

A total of 100 patients were enrolled in this study. Among the study population, 50 were control group (patients treated with only conventional medical management of chronic heart failure), and 50 were experimental group (patients treated with ivabradine plus conventional medical management of chronic heart failure.). The mean age in the control group was 56.56 ± 14.86 (SD), and in the experimental group was 58.60 ± 9.84 (SD). Among the study subjects, 69% were male, and 31% were female. The male: female ratio was almost 2:1.

**Table I: Baseline characteristics of study populations**

| Baseline characteristics | Study groups | |
|---|---|---|
| | Control group n =50 | Experimental group n =50 |
| **Age** | 56.56 ± 14.86 | 58.60 ± 9.84 |
| **Gender** | | |
| Male | 36 (72%) | 33 (66%) |
| Female | 14 (28%) | 17 (34%) |
| **BMI** | 23.38 ± 2.51 | 22.94 ± 2.87 |
| **Smoking Status** | | |
| Smoker | 8 (16%) | 12 (24%) |
| Nonsmoker | 37 (74%) | 27 (54%) |
| Ex-smoker | 5 (10%) | 11 (22%) |
| **NYHA classification of heart failure** | | |
| Class II | | |
| Class III | 58% | 38% |
| Class IV | 32% | 40% |
| | 10% | 22% |

Except for heart rate during the second follow-up visit ($p < 0.001$), the mean (±SD) difference between both study groups of different variables like duration of CHF in weeks, number of previous hospitalizations, SBP in mm of Hg, DBP in mm of Hg, baseline heart rate/min during enrolment, during first follow-up visit were statistically not significant ($p > 0.05$).

**Table II: Comparison of the mean difference between the study groups about various parameters of the chronic heart failure respondents.**

| Variables | Study Group | N | Mean | Std. Deviation | t | p |
|---|---|---|---|---|---|---|
| Duration of CHF in Weeks | Control | 50 | 14.14 | 18.72 | 0.51 | > 0.05 |
| | Experimental | 50 | 15.86 | 14.91 | | |
| Number of previous hospitalizations | Control | 50 | 1.46 | 1.33 | 1.28 | > 0.05 |
| | Experimental | 50 | 1.82 | 1.44 | | |
| SBP in mm of Hg | Control | 50 | 119.80 | 25.91 | 0.02 | > 0.05 |
| | Experimental | 50 | 119.70 | 23.57 | | |
| DBP in mm of Hg | Control | 50 | 75.90 | 17.89 | 0.31 | > 0.05 |
| | Experimental | 50 | 77.00 | 17.29 | | |
| Baseline heart rate/min during enrolment | Control | 50 | 106 | 20 | 0.15 | > 0.05 |
| | Experimental | 50 | 106 | 19 | | |
| Heart rate/min during 1st follow-up visit | Control | 48 | 89 | 9 | 1.47 | > 0.05 |
| | Experimental | 49 | 86 | 9 | | |
| Heart rate/min during second follow-up visit | Control | 46 | 77 | 5 | 7.73 | <0.001 |
| | Experimental | 49 | 70 | 4 | | |

The comparison of mean score differences of Minnesota living with heart failure questionnaire (MLWHFQ) during baseline, first & second follow-up visits between the study groups of the respondents with chronic heart failure. The baseline MLWHFQ score was proportionately higher (Mean MLWHFQ score between experimental vs. control = 55.70 vs. 53.40) among the experimental than the control group during enrolment. However, during the first and second follow-up visits, it was less among the respondents of the experimental group than the control group (Mean MLWHFQ score between the experimental vs. control group during the first and second visit = 38.84 vs. 46.98 and 25.80 vs. 41.61 respectively). Independent samples t-tests were used to compare the mean (± SD) differences of MLWHFQ scores between the control (n=50) and experimental (n=50) groups of respondents with chronic heart failure. Shapiro-Wilk statistic was non-significant, indicating that the assumption of normality was not violated and Levene's test was not significant; thus, an equal variance can be assumed for both groups for all three follow-up occasions. Except for MLWHFQ score during baseline [$t(100) = 0.60$ $p > 0.05$], mean (±SD) differences of MLWHFQ scores during the first & second follow-up visits between the two drugs therapy groups were statistically significant [$t(100) = 2.43$ $p < 0.05$, two-tailed & $t(100) = 6.60$ $p < 0.001$ two-tailed respectively].

**Table III: Comparison of mean score difference of Minnesota living with heart failure questionnaire (MLWHF) during baseline, first & second follow-up visits between the study groups of the chronic heart failure respondents.**

| MLWHF score | Study Group | N | Mean | Std. Deviation | t | p |
|---|---|---|---|---|---|---|
| Minnesota living with heart failure questionnaire baseline score | Control | 50 | 53.40 | 17.40 | 0.60 | > 0.05 |
| | Experimental | 50 | 55.70 | 21.51 | | |
| Minnesota living with heart failure questionnaire score during the first follow-up visit | Control | 46 | 46.98 | 13.47 | 2.43 | < 0.05 |
| | Experimental | 49 | 38.84 | 18.93 | | |
| Minnesota living with heart failure questionnaire score during the second follow-up visit | Control | 46 | 41.61 | 11.40 | 6.60 | < 0.001 |
| | Experimental | 49 | 25.80 | 11.94 | | |

t (100) = 0.60 p = .551 two-tailed 95% CI -10.10 ,5.42 mean difference -2.34

t (100) = 2.43 p = .017 two-tailed 95% CI 1.47,14.81 mean difference 8.14

t (100) = 6.60 p = .000 two-tailed 95% CI 11.05 ,20.57 mean difference 15.81

Distribution of baseline quality of life of both CHF study groups (n=100). It reveals that among the control group, 33 (66 %) respondents had poor quality of life, and among the experimental group, 34 (68 %) respondents had poor quality of life.

**Table IV: Distribution of baseline quality of life of both study group CHF respondents (n = 100).**

| Baseline quality of life of the experimental group CHF respondents | Study groups | |
|---|---|---|
| | Control group | Experimental group |
| | Frequency (Percentage) | Frequency (Percentage) |
| Good quality of life | 2 (04) | 2 (04) |
| Moderate quality of life | 15 (30) | 14 (28) |
| Poor quality of life | 33 (66) | 34 (68) |
| **Total** | **50 (100)** | **50 (100)** |

*MLWHFQ score cut point for the assessment of the quality of life of CHF patients

< 24 = Good quality of life, 24-45 Moderate quality of life, and > 45 = Poor quality of life

Distribution of quality of life of both CHF study groups respondents during the first follow-up visit (n=100). It reveals that among the control group, 25 (50 %) respondents had poor quality of life, 20 (40%) had moderate quality of life, and only 1 (2%) respondent had good quality of life. During this follow-up period, four (8%) respondents were dead, but improvement in quality of life from poor to moderate quality was also observed among the experimental group; 15 (30 %) respondents had poor quality of life, 20 (40%) had a moderate quality of life and 14 (28%) had a good quality of life, and during this follow-up period, only 1(2 %) respondent was dead but far better improvement of quality of life implied by shifting

from poor to moderate & good quality of life also observed than control group respondents after the first month of therapy.

**Table V: Distribution of quality of life of both study group CHF respondents during their first follow-up visit (n = 100).**

| Quality of life of the study group during the first follow-up visit | Study groups | |
|---|---|---|
| | Control group | Experimental group |
| | Frequency (Percentage) | Frequency (Percentage) |
| Good quality of life | 1 (02) | 14 (28) |
| Moderate quality of life | 20 (40) | 20 (40) |
| Poor quality of life | 25 (50) | 15 (30) |
| Total | 46 (92) | 49 (98) |
| Death | 4 (08) | 1 (02) |
| **Total** | **50 (100)** | **50 (100)** |

Distribution of quality of life of both study groups during their second follow up visit (n=100). It reveals that among the control group, 13 (26 %) of the respondents had poor quality of life, 30 (60%) had a moderate quality of life, and only 3 (6%) had a good quality of life after 12 weeks of drug therapy. Up to this follow-up period, no more death occurred, and better improvement in quality of life was observed. Among the experimental group, 6 (12 %) respondents had poor quality of life, 18 (36 %) had moderate quality of life, and 25 (50 %) had good quality of life after 12 weeks of drug therapy. Up to this follow-up period no more death, and had far better improvement in quality of life in comparison to control group respondents.

**Table VI: Distribution of quality of life of both study group CHF respondents during their second follow-up visit (n = 100).**

| Quality of life of the study group during the second follow-up visit | Study groups | |
|---|---|---|
| | Control group | Experimental group |
| | Frequency (Percentage) | Frequency (percentage) |
| Good quality of life | 3 (06) | 25 (50) |
| Moderate quality of life | 30 (60) | 18 (36) |
| Poor quality of life | 13 (26) | 6 (12) |
| Total | 46 (92) | 49 (98) |
| Death | 4 (08) | 1 (02) |
| **Total** | **50 (100)** | **50 (100)** |

## Discussion

A total of 100 patients were enrolled in this study. Among the study population, 50 were control group-(patients who were treated with only conventional medical management of chronic heart failure), and 50 were experimental group (patients who were treated with Ivabradine plus conventional medical management of chronic heart failure.). The mean age in the control group was 56.56 ± 14.86 (SD), and in the experimental group was 58.60 ± 9.84 (SD). Among the study subjects, 69% were male, and 31% were female. The male: female ratio was almost 2:1.

In this study, among the control group mean (± SD) BMI of the respondents was 23.38 (±2.51),

the mean duration of CHF was 14.14 (±.18.72) weeks, and the mean (± SD) frequency of previous hospital admission was 1.46 (± 1.33) times. The mean (± SD) systolic & diastolic blood pressure were 119.80 ± 25.91 & 75.90 ± 17.89, respectively, and the mean (± SD) heart rates during enrollment, after four weeks, and after 12 weeks of drugs therapy were 105 (± 20), 89 (± 9) & 77 (±5) respectively. Again, the distribution of different variables of the experimental group revealed that the mean (± SD) BMI of the respondents was 22.94 (±2.87), the mean duration of CHF was 15 (±.16.86) weeks, the mean (± SD) frequency of previous hospital admission was 1.82 (± 1.44) times, mean (± SD) systolic & diastolic blood pressure were 119.70 ± 23.57 & 77.00 ± 17.29 respectively. The mean (± SD) heart rates during enrollment, after four weeks, and after 12 weeks of drugs therapy were 106 (± 19), 86 (± 9) & 70 (± 4), respectively. A comparison of the mean (±SD) differences of different variables was made, but there was no significant difference between the two study groups with respect to baseline demographic and clinical characteristics except heart rate during the second follow-up visit ($p < 0.001$), which was found statistically significant.

A study demonstrated the baseline mean (±SD) HR, systolic, and diastolic blood pressure among the control group was 94.6 ± 8.7 bpm, 124.3± 13.8 & 78.9± 10 mm of Hg, respectively. Again, the baseline mean (±SD) HR, systolic, and diastolic blood pressure among the ivabradine group were 95.3 ± 11.04 bpm, 124.4±15.6 & 78.9 ± 10.9 mm of Hg, respectively. There was no significant difference between the ivabradine and control group with respect to baseline demographic, clinical characteristics, and medications but heart rate after three months of treatment was significantly lower in the ivabradine group ($p=0.01$), which was quite similar to the present study.[6] In this study mean (± SD) MLWHFQ score of the control group during enrollment was 53.40 (±17.40), which reduced to 46.98 (± 13.47) during the first follow-up visit after four weeks, and it was further reduced to 41.61 (±11.40) during a second follow-up visit after 12 weeks. Again, the mean (± SD) of the MLWHFQ score of the experimental group respondents during enrollment was 55.74 (±21.51), which reduced to 38.84 (± 18.93) during the first follow-up visit and further reduced to 25.80 (±11.94) during the second follow-up visit. The comparison of differences of the mean (± SD) of MLWHFQ score between two study groups at first and second follow-up visits were statistically significant [$t (100) = 2.43$ $p < .05$, two-tailed & $t (100) = 6.60$ $p < 0.001$ two-tailed respectively].

A prospective randomized controlled Trial demonstrated that the baseline mean (±SD) of MLWHFQ score was 77.9 ± 7.6 among the control group and 78.4 ± 8.4 for the Ivabradine group. After three months, the ivabradine group had significantly lower MLWHFQ scores as compared to the control group (58.3 ± 10.2 vs. 71.4± 11.2, $p < 0.001$).[6] These findings are similar to the present study. Another study shows that the mean values for MLWHFQ were 56.9 ± 18.2 and 49.9 ± 22.3 at baseline in the beta-blocker (BB) alone group and a beta-blocker (BB) + ivabradine group and at 12 months of follow-up, these values reduced to 48.5 ± 15.8 ($p =0.01$) and 29.5 ± 15.3 ($p = 0.0001$) respectively.[7] So, they also observed significantly greater improvement in the QOL from admission to 12 months of treatment with BB+ ivabradine than BB alone ($p < 0.05$).

According to the MLWHFQ cut point, it was observed that poor baseline quality of life gradually shifted to good quality of life and was proportionately higher in the experimental group than in the control group respondents after four weeks and 12 weeks of treatment. Relations between the respondents of both study groups of chronic heart failure and their different quality of life (n=100) during the first follow-up visit ($p < 0.05$) and second follow-up visit ($p < 0.001$) were statistically significant. So far, I explored that very little published scientific literature has been found to compare all the variables of interest of the present study between two groups of CHF patients using MLWHFQ score and their cut point-based category of qualities of life.

Different studies had conducted in many countries and regions with so many other scales for assessing the quality of life among patients of

chronic heart failure with different drugs as well as similar medical management. Riccioni[8] used the SF-36 questionnaire, Zugck[5] used the European quality of life-5 dimensions (EQ-5D) QOL index, and Ekman[1] used Kansas City Cardiomyopathy Questionnaire (KCCQ) score. Like the present study, the above-mentioned studies also showed that HR reduction by ivabradine was associated with a significant increase in QOL.

In this study, irrespective of baseline data of both study groups, statistically significant ($p < 0.05$) improvements in heart rate, MLWHFQ score, improved quality of life were noted in the respondents treated with ivabradine plus conventional medical management than only conventional medical management group in both the first and, second follow-up visit. So, the findings implied that the null hypothesis was rejected, but an alternative hypothesis was accepted in the present study, which was also similar to many previous studies. So, the addition of ivabradine to conventional medical management in treating patients with chronic heart failure improves their symptoms, quality of life, and heart rate. Ultimately reducing the morbidity and mortality of such patients.

## Conclusion

In patients with chronic heart failure, the addition of ivabradine to conventional medical management might be helpful in the improvement of their symptoms, quality of life, and heart rate.

**Conflict of interest:** None declared.

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