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Assessing the Efficacy and Safety of Ivabradine as Adjunctive Therapy in Acute Heart Failure: A Prospective Clinical Trial

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ABSTRACT

Objective: To compare the clinical outcome in terms of efficacy and safety of Ivabradine as adjunctive therapy in patients with acute heart failure.

Methodology: A prospective clinical trial was conducted involving patients admitted with acute heart failure, who were randomized to receive either standard care alone or standard care with adjunctive Ivabradine therapy. Efficacy endpoints included improvement in symptoms, left ventricular ejection fraction (LVEF), and reduction in heart rate. Safety endpoints encompassed adverse events, including bradycardia and hypotension. Data were collected at baseline, during treatment, and at follow-up visits.

Results: The mean age (67.5 vs. 68.2 years), Gender distribution, mean ejection fraction (35.7 ± 5.2 vs 36.1 ± 4.8), NYHA class, and prevalent comorbidities were comparable between both groups. The mortality rate (10% vs. 15%), and hospital readmissions (20% vs. 30%, p=0.12) showed no significant difference between both groups. The improvement in NYHA class (65% vs. 50%, p=0.04) was significantly (P-value > 0.05) higher in the treatment group. Treatment group demonstrated a significantly greater increase in ejection fraction (mean change 4.8% vs. 2.3%, p<0.001). Clinical outcomes, heart rate reduction, 6-minute walk distance, reduction in NT-proBNP, all-cause mortality and rate of heart failure hospitalizations were found significantly (p-value < 0.05) better in treatment group.

Conclusion: This prospective clinical trial suggests that Ivabradine as adjunctive therapy in acute heart failure is efficacious in improving symptoms and reducing heart rate, with a favorable safety profile. These findings support the consideration of Ivabradine as an adjunctive treatment option in acute heart failure management.

Keywords: Ivabradine, Acute heart failure, adjunctive therapy, clinical trial, efficacy, safety.

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Introduction

Acute heart failure (AHF) poses a major worldwide health problem, with high death rates and many hospital stays. Current AHF treatments aim to ease symptoms, boost heart function, and tackle other health issues. Yet even with better medical care many AHF patients still face adverse outcome. This calls for new add-on treatments to improve patient prognosis.[1]

Heart failure is a severe illness that presents with symptoms including exhaustion, congestion, and dyspnoea because the heart cannot pump blood fast enough to satisfy the body's demands. The advancement in treatment options has not reduced the number of people suffering from heart failure which is the worldwide leading cause of morbidity and mortality. Specifically, in patients with acute heart failure, frequent

worsening episodes particularly, come with considerable treatment risks and complications.[2]

Over time, there seems to have been great focus in the search for new treatment options to optimize the outcomes in acute heart failure. One of them is Ivabradine, which reduces the firing rate of the pacemaker cells in the sinoatrial node that decreases heart rate but does not have deleterious inotropic effect. Due to the mechanism of action, Ivabradine is very favourable treatment for heart failure especially in patients with elevated heart rate and decreased cardiac effectiveness.[3] This drug was approved by the authorities for this purpose after trials demonstrated that Ivabradine was good to slow the rate of heart for patients suffering from chronic heart failure.[4]

Ivabradine, which blocks if channels show potential to slow heart rate without hurting heart strength or blood pressure. This sets it apart from standard beta-blockers. It targets the heart's natural pacemaker slowing heart rate and giving the heart more time to fill with blood. This might help ease heart failure symptoms. Research has shown it works well for long-term heart failure, but we know less about how it helps with sudden severe heart failure.[5,6]

Ivabradine is under study in acute heart failure since it has the potential of enhancing haemodynamic status and relieve symptoms by interfering tachycardiagenic effects and ensuring the supply-demand balance for oxygen in the heart.[7] Therapeutically, ivabradine acts selectively on heart rate, thus being a newest method of treatment in addition to the usual treatments like diuretics, vasodilators, and inotropic medications.[8]

Several considerations like side effects, primary and secondary endpoints, dose schedules and patient inclusion/exclusion are important for the safety profile and efficacy of ivabradine as an additional therapeutic tool for acute heart failure.[9] These outcomes should include long-term objectives such as readmission rates and mortality and short-term objectives, including stable hemodynamic as well as alleviation of symptoms.[10]

This study was planned to evaluate the efficacy and safety of ivabradine as a treatment for patients with sudden heart failure. By looking at how it controls heart rate affects patient health, and any side effects, this study aims to shed light on how ivabradine could make treatment better for acute heart failure.

Methodology

This randomized comparative study was conducted in the department of Cardiology Gajju Khan Medical College Swabi, over a period of two years' form June 2022 to June 2024. The patients enrolled in the study were patients who admitted with heart failure. The study was started by taking approval of the study from Institutional Review Boards (IRBs)/ Ethics Committee. All the patients who fulfilled the inclusion exclusion criteria were selected by non-probability consecutive sampling technique. Inform written consent was taken from the guardian of the patient at the time of inclusion in the study.

Patients with acute heart failure having age above 18 years, both genders; who had been clinically diagnosed with heart failure, and who complied with the research protocol were included in the study. While patients receiving Ivabradine were excluded due to contraindication to its use. Similarly, patients diagnosed with major comorbidities, and those who could not give informed consent were also excluded. Sample size was calculated with help of WHO sample size calculator using 5% level of significance, 80% power of study, 3.2 population standard deviation and anticipated population mean value of SBP of 12 mmHg, with Ivabradine and 11.1 in control group [e]. The sample size turned to be 200 patients dividing into two equal groups of 100 patients each.

The patients were divided into two groups. The treatment group patients received Ivabradine alongside other conventional treatments for managing heart failure while the patients in the control group received placebo along with standard protocol treatment plan. The initial dose of Ivabradine was 5 mg, twice a day and was adjusted after 2 weeks based on the heart rate of the patients up to a maximum dose of 7.5 mg.

The patients' demographic and clinical characteristics were recorded at the time of enrolment in the study. The information regarding ejection fraction, NYHA classification, comorbidities were noted on a predesigned perfoma. All the patients were followed up for 30 days and during this period information for readmission rate, improvement in NYHA classification, increase in ejection fraction, adverse events, heart rate reduction (bpm), 6-minute walk distance (meters), reduction in NT-proBNP (pg/mL) within 30 days was noted among all the patients in both groups.

All the collected data was entered and analyzed with the help of SPSS v. 25. Descriptive statistics such as mean

and standard deviation were used for quantitative data and for comparison between groups independent sample t-test was applied. Qualitative data was presented with frequqncy and percentage and comparison between groups was made with chi-square tests. P-value < 0.05 was considered significant.

Results

The mean age (67.5 vs. 68.2 years) of participants was similar (P-value > 0.05) in both groups, with no statistically significant difference. Gender distribution, mean ejection fraction (35.7 ± 5.2 vs 36.1 ± 4.8), NYHA class, and prevalent comorbidities such as hypertension, diabetes, coronary artery disease (CAD), and chronic obstructive pulmonary disease (COPD) were also comparable between the groups, without having statistically significant (p-value > 0.05) difference as elaborated in table 1.

Table 1. Baseline Characteristics of Patients

Characteristic	Treatment Group (n=100)	Control Group (n=100)	P-value
Age (years)			
(Mean ± SD)	67.5 ± 8.3	68.2 ± 7.9	0.45
Gender			
Male	60	58	0.75
Female	40	42	
Ejection Fraction (%)			
Mean ± SD	35.7 ± 5.2	36.1 ± 4.8	0.30
NYHA Class			
II	40%	38%	0.65
III	50%	52%	
IV	10%	10%	
Comorbidities			
Hypertension	60%	62%	> 0.05
Diabetes	30%	28%	> 0.05
CAD	25%	27%	> 0.05
COPD	15%	16%	> 0.05

Table 2, showed the comparison of clinical outcomes at the 30-day follow-up. The mortality rate in the treatment group was numerically lower than in the control group (10% vs. 15%), although this difference did not reach statistical significance (p=0.21). Similarly, although not statistically significant, there was a trend towards reduced hospital readmissions in the treatment group compared to the control group (20% vs. 30%, p=0.12). The improvement in NYHA class (65% vs. 50%, p=0.04) was significantly higher in the treatment group compared to the control group. This indicates that patients receiving Ivabradine as adjunctive therapy had a better outcome. Additionally, the treatment group demonstrated a significantly greater increase in ejection fraction (mean change 4.8% vs. 2.3%, p<0.001) compared to the control group, highlighting the positive effect of Ivabradine on cardiac function.

Table 2. Clinical Outcomes at 30 Days

Outcome	Treatment Group (n=100)	Control Group (n=100)	p-value
Mortality Rate (%)	10	15	0.21
Hospital Readmissions (%)	20	30	0.12
Improvement in NYHA Class (≥1 Class) (%)	65	50	0.04
Increase in Ejection Fraction (%) (Mean ± SD)	4.8 ± 2.1	2.3 ± 1.8	<0.001
Adverse Events (%)	25	20	0.32

To comparison of clinical outcome was made based on heart rate reduction (bpm), 6-minute walk distance (meters), reduction in NT-proBNP (pg/mL), all-cause mortality (%) and rate of heart failure hospitalizations (%) between treatment group and control group. The comparison of heart Rate Reduction (bpm) Ivabradine significantly reduces heart rate by 15±3 bpm compared to a 5±2 bpm reduction in the control group, with a p-value <0.001. Among patients of Ivabradine group a significantly ((320 meters vs. 290 meters, p=0.01)) higher improvement in their 6-minute walk distance was noted as compared to group. Similarly, patients in Ivabradine group shows a significantly (p-value <0.001) greater reduction in NT-proBNP levels (800 pg/mL) compared to the control group (600 pg/mL). The Ivabradine group also had a lower all-cause mortality rate (10%) compared to the control group (18%), with a statistically significant p-value of 0.04. The rate of hospitalizations due to heart failure were observed significantly (p-value < 0.05) lower in the Ivabradine group (15%) in comparison to the Placebo group (25%) as elaborated in table 3.

Table 3. Comparison of outcome variables between both groups

Parameter	Treatment Group (n=100)	Control Group (n=100)	p-value
Heart Rate Reduction (bpm)	15 ± 3	5 ± 2	<0.001
6-Minute Walk Distance (meters)	320 ± 50	290 ± 45	0.01
NT-proBNP Reduction (pg/mL)	800 ± 100	600 ± 80	<0.001
All-Cause Mortality (%)	10	18	0.04
Heart Failure Hospitalizations (%)	15	25	0.03

Discussion

In this prospective clinical trial assessing the efficacy and safety of ivabradine as adjunctive therapy in acute heart failure (AHF), the findings of this study will help in understanding the potential role of Ivabradine in heart rate reduction for the management of heart failure. Ivabradine, known for selectively inhibiting the IF current in the sinoatrial node, was evaluated in terms of its impact on heart rate, hemodynamic stability, and patient outcomes when used alongside standard heart failure therapy.[11,12]

Our study demonstrated a significant reduction in heart rate among patients receiving ivabradine in comparison to those treated with standard therapy alone. This result aligns with previous studies, such as the SHIFT trial, which highlighted the benefits of ivabradine in reducing hospitalization and improving outcomes in chronic heart failure patients with elevated heart rates. In the context of AHF, where elevated heart rate is a known risk factor for adverse outcomes, our results suggest that ivabradine can be beneficial in managing this acute presentation.[13]

When using ivabradine it was anticipated reduce the heart rate while not provoking myocardial contractility since it selectively inhibits the If current from sinoatrial node. This might help reduce haemodynamic load on the struggling heart to some extent. In this particular trial, the results obtained demonstrated that participants in the sample, who took ivabradine, had a reduced heart rate compared to the control group with significance of $p<0.05$. Persistent or worsening of such signs such as weariness and dyspnoea was associated with this drop in heart rate thus implying amelioration on the clinical status of AHF patients.[14,15]

Furthermore, patients in the ivabradine group showed improvement in left ventricular function, measured through reductions in NT-proBNP levels and improvements in ejection fraction (EF). This supports the hypothesis that heart rate reduction can alleviate myocardial oxygen demand and improve diastolic filling time, thereby enhancing cardiac performance in patients with AHF.[16,17]

The safety of ivabradine in acute heart failure is a critical aspect of this study, as the drug's negative chronotropic effect could theoretically lead to hemodynamic instability in vulnerable patients. However, ivabradine was well-tolerated in our study population, with no significant increase in adverse events such as bradycardia, hypotension, or syncope. Importantly, no patients discontinued the drug due to adverse reactions, and there were no instances of excessive bradycardia (heart rate <50 bpm), which could compromise hemodynamics [18].

Our findings are consistent with previous reports that suggest ivabradine is generally safe when used in patients with heart failure, provided careful monitoring of heart rate and blood pressure is performed. The lack of significant side effects also suggests that ivabradine could be incorporated safely as an adjunct to standard therapy for AHF, especially in patients with heart rates >70 bpm, as outlined in heart failure management guidelines.[19,20]

Conclusion

In conclusion, this study demonstrates that ivabradine, as adjunctive therapy in the treatment of AHF, can effectively reduce heart rate without compromising patient safety. The observed improvements in left ventricular function and overall clinical outcomes suggest that heart rate reduction may be a valuable target in the acute setting. However, larger trials with longer follow-up periods are needed to confirm these findings and fully establish the role of ivabradine in AHF management.

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