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# Effect of Ivabradine in Controlling Heart Rate in Patients with Sepsis and Septic Shock: Randomized Control Trails

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**Abstract**

*Background:* Ivabradine is a selective inhibitor of ($I_f$) channels in the sinoatrial node and a pure bradycardic agent with no deleterious effect on other aspects of cardiac function nor on blood pressure. This study was conducted to evaluate the effect of Ivabradine on controlling tachycardia in sepsis patients as compared to placebo. *Methods:* A total of 100 patients admitted to the Medical Intensive Care Unit (MICU) were recruited in this randomized controlled trial. A total of 50 patients were randomly allocated to either Group A (the Ivabradine group) or Group B (the control group). Heart rate (HR) was recorded for all patients at baseline, 12, 24, 48, 72, 96, and 120 hours. Mean arterial pressure (MAP), ejection fraction (EF), and change in Norepinephrine (NE) dosage were recorded at baseline and post-intervention (120 hours). A mortality rate was recorded for both groups. *Results:* The patients had a mean age of 32.49 $\pm$ 16.22 years. There were 56 males and 44 females in the study. Epilepsy (n = 12, 12%) and tetanus (n = 11, 11%) were the most common primary diagnosis. Ventilator Associated Pneumonia (n = 60) was found to be the most common infection. Patients in Group A (23.2 $\pm$ 11.02 beats per minute) had a significantly greater heart rate reduction at 120 hours in mean heart rate as compared to Group B patients (8.92 $\pm$ 30.46 beats per minute, p = 0.002). The increase in mean MAP for Group A (1.68 $\pm$ 2.44 mm Hg) was also significantly greater than that for Group B (0.54 $\pm$ 2.46 mm Hg, p = 0.022). There was no difference in the mean change in NE dosage between Groups A (0.63 $\pm$ 0.25 units/minute) and B (-0.34 $\pm$ 0.36 units/minute, $p$ = 0.106). A significantly greater increase in EF was found for Group A (1.16 $\pm$ 1.5%), in comparison to Group B (0.30 $\pm$ 1.69 %, p = 0.009). There were 22 (44%) deaths reported in Group A as compared to 24 (48%, $p$ = 0.688) in Group B. *Conclusion:* Ivabradine has a significantly greater effect on controlling heart rate as compared to placebo in sepsis patients. The use of Ivabradine should be included in clinical guidelines for managing sepsis patients in ICU settings.

*Keywords:* Ivabradine; Sepsis; Septic-Shock; Tachycardia; SIRS.

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## 1. Introduction

Sepsis is a critical medical condition characterized by a systemic response of the immune system to an infection, culminating in a life-threatening state that can ultimately progress to irreversible, terminal organ dysfunction [1]. In Intensive Care Units (ICUs), sepsis remains one of the primary causes of mortality, as supported by studies conducted by notable sources [2]. Despite significant efforts to combat sepsis by targeting its diverse underlying abnormalities, these endeavours have, for the most part, yielded limited success. Sepsis is characterized by tachycardia, which may be caused by a variety of factors such as increased body temperature, decreased blood volume, increased sympathetic tone, and/or exogenous catecholamines [3, 4]. In severe sepsis and septic shock, tachycardia has been identified as an independent risk factor for mortality regardless of core body temperature, suggesting that the heart rate response to sepsis may be an adaptive mechanism to sustain oxygen delivery [5]. Heart rate serves as a well-established parameter for assessing the severity of sepsis and is incorporated into various scoring systems utilized to predict mortality risk, including the Simplified Acute Physiological Score 3 (SAPS3) and the Acute Physiology and Chronic Health Evaluation II (APACHE-II) system, among other validated approaches [6]. Furthermore, heart rate is an integral component of the diagnostic criteria for Systemic Inflammatory Response Syndrome (SIRS) [6].

Tachycardia represents a significant risk factor for diverse cardiovascular events. An elevated heart rate (HR) or uncontrolled tachycardia substantially augments myocardial oxygen consumption while concurrently diminishing diastolic perfusion time. This effect is particularly pronounced in sepsis and Systemic Inflammatory Response Syndrome (SIRS) scenarios [7]. Furthermore, tachycardia can elevate ventricular diastolic pressures, predisposing individuals to ventricular arrhythmias and potentially manifesting as systolic or diastolic heart failure [8]. These circumstances place critically ill patients at risk of stress-induced cardiac dysfunction resulting from heightened sympathetic activity, which subsequently contributes to the development of tachycardia [9].

Recent research has demonstrated that beta-blockers are useful for controlling heart rate in septic shock, improving hemodynamics and prognosis [10, 11]. Patients with left ventricular systolic dysfunction, a disease that may require the use of -adrenergic medications, may find it challenging to take -blockers clinically routinely during septic shock due to their unfavorable inotropic and hypotensive effects [12].

Ivabradine is a new selective negative chronotropic drug that blocks the Sodium funny channels ($I_f$). It lowers the heart rate by reducing the diastolic depolarization slope. At the same time, ivabradine does not affect the sympathetic pathways; therefore, it does not interfere with inotropic agents [13].

Ivabradine, a selective inhibitor of $I_f$ channels in the sinoatrial node, has no adverse effects on inotropic function or arterial load, whereas beta-blockers do [14]. Endothelial function, microvascular perfusion, and inflammation are probably all improved by ivabradine as well [15]. Patients with chronic left ventricular systolic dysfunction and tachycardia benefit from ivabradine's anti-ischemic actions and enhanced clinical results [15].

The drug inhibits the pacemaker $I_f$ current in a dose-dependent manner at concentrations that do not interfere with other cardiac ion currents. When this channel is inhibited, cardiac pacemaker activity is reduced, lowering the heart rate and thus allowing more time for blood to flow to the heart muscle [16]. The major adverse effects of ivabradine include luminous phenomena, atrioventricular block, ventricular extra-systole and bradycardia [17].

Ivabradine acts as a selective negative chronotropic agent and was initially employed in clinical settings for patients afflicted with symptomatic stable coronary disease, aiming to diminish myocardial oxygen demand [18]. It was found in various studies that ivabradine was effective in chronic stable angina, specifically among all the coronary artery diseases [19]. Nevertheless, the current clinical evidence supporting this hypothesis remains insufficient for practical application. Therefore, this randomized controlled study aimed to evaluate the effects of Ivabradine in patients admitted to a hospital setting with sepsis or septic shock as compared to a placebo.

## 2. Materials and Methods

### 2.1. Study Design and Setting

This was a single-center, parallel-arm randomized controlled trial carried out at the medical intensive care unit (MICU) of a tertiary care hospital named PIMS (Pakistan Institute of Medical Sciences) and Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, Pakistan.

### 2.2. Study Participants

Patients admitted to the MICU who developed sepsis were included in the trial. The following selection criteria were used for recruiting the participants:

### 2.3. Eligibility Criteria

Patients aged between 14 and 70 years of both genders (male and female) who had consecutive patients with septic-shock or sepsis. A heart rate (HR) of greater than 95 per minute with or without the use of vasopressor agents was included in the study.

All those patients having a known allergy to ivabradine or already receiving other rate-controlling drugs for other pathologies with a history of visual disturbances, along with histories of AV blocks of any degree and cardiac arrhythmias other than AV blocks and temporary or permanent cardiac pacemakers, were excluded from the study.

### 2.4. Sample Size

The WHO sample size calculator was used for sample size calculations. The minimum heart rates from the study by Andreas et al. were used for the sample size calculation. At a 5% level of significance with 80% power, in order to estimate a comparison between the population heart rate of 68.9 + 12.9 bpm and an anticipated heart rate of 63.1, a sample size of 78 patients was estimated to be adequate. A total of 100 patients in sepsis or septic shock with a heart rate greater than 95 per minute with or without the use of nor-epinephrine agents to maintain a mean arterial pressure greater than 65 mm Hg.

### 2.5. Randomization

Patients were divided into two groups of 50 participants, each selected according to the minimization method. Group A participants were given Ivabradine to control heart rate, whereas Group B patients were not given any drug to control heart rate.

### 2.6. Interventions

After taking written, informed consent from all eligible patients, they were randomized according to the minimization method to either Group A or B. The two groups were defined as follows:

1) *Group A* – Ivabradine treatment regimen group who received ivabradine via nasogastric tube at a dose of 7.5 mg at 12-hour intervals for 48 hours after a first loading dose of 10 mg and then 5 mg at 12-hour intervals for a total of five days.

2) *Group B* – Control treatment regimen group who received no treatment to control the heart rate.

Both study groups were administered the appropriate treatment following the guidelines outlined in the Surviving Sepsis Guidelines 2017 Management, specifically addressing the management of sepsis and septic shock. Hemodynamic support was provided through the administration of vasopressor and ionotropic agents alongside antibiotics, as well as the insertion of central venous catheters and arterial catheters to monitor hemodynamic parameters.

Throughout the course of therapy, all patients underwent echocardiography evaluations before treatment initiation, during treatment, and after therapy initiation. Heart rate assessments were recorded at specific time points, including 0, 12, 24, 48, 72, 96, and 120 hours. Furthermore, the study examined any potential impact on mean arterial pressure during the therapeutic window, along with any reduction in the need for vasopressor agents. These analyses were conducted at corresponding time intervals for both study groups.

### 2.7. Study Outcome

#### 2.7.1. Primary Outcomes

The following variables were measured as primary study outcomes:

Heart rate (measured at 0, 12, 24, 24, 48, 72, 96, and 120 hours) and mean arterial pressure (measured at 0 and 120 hours, pre- and post-intervention measurements). The dosage of vasopressor agents (measured at 0 and 120 hours pre- and post-intervention measurements). Ejection fraction (measured at 0 and 120 hours – pre- and post-intervention measurements) and SAPS III Scores (measured at baseline).

#### 2.7.2. Secondary Outcomes

Mortality was the only secondary outcome evaluated. All the patients were followed up to their discharge from the ICU, death during the ICU stay, and for those who were neither discharged nor died, for seven days.

### 2.8. Data Analysis

The Data was analyzed using SPSS version 26. Heart rate was measured in both groups at 0, 12, 24, 48, 72, 96, and 120 hours. The mean change in heart rate as compared to the 0 hour measurement was calculated for 24, 48, and 120 hours. The mean change in heart rate between the two groups was compared between the two groups at 24, 48, and 120

hours. The mean HR at each time interval and changes in HR, MAP, EF, and norepinephrine dosage were compared by applying the independent sample T test. Moreover, in order to compare the mean ages and SAPS III scores between the two groups, an independent sample T test was applied. The frequency of gender distribution was compared by applying the chi-squared ($X^2$) test. An arbitrary value of $< 0.05$ was considered to be significant.

## 2.9. Ethical Approval

After obtaining clearance from the Institutional Ethics Committee, the study commenced. The participation of the patients in this study was entirely voluntary. Prior to enrolment, each participant provided signed informed consent.

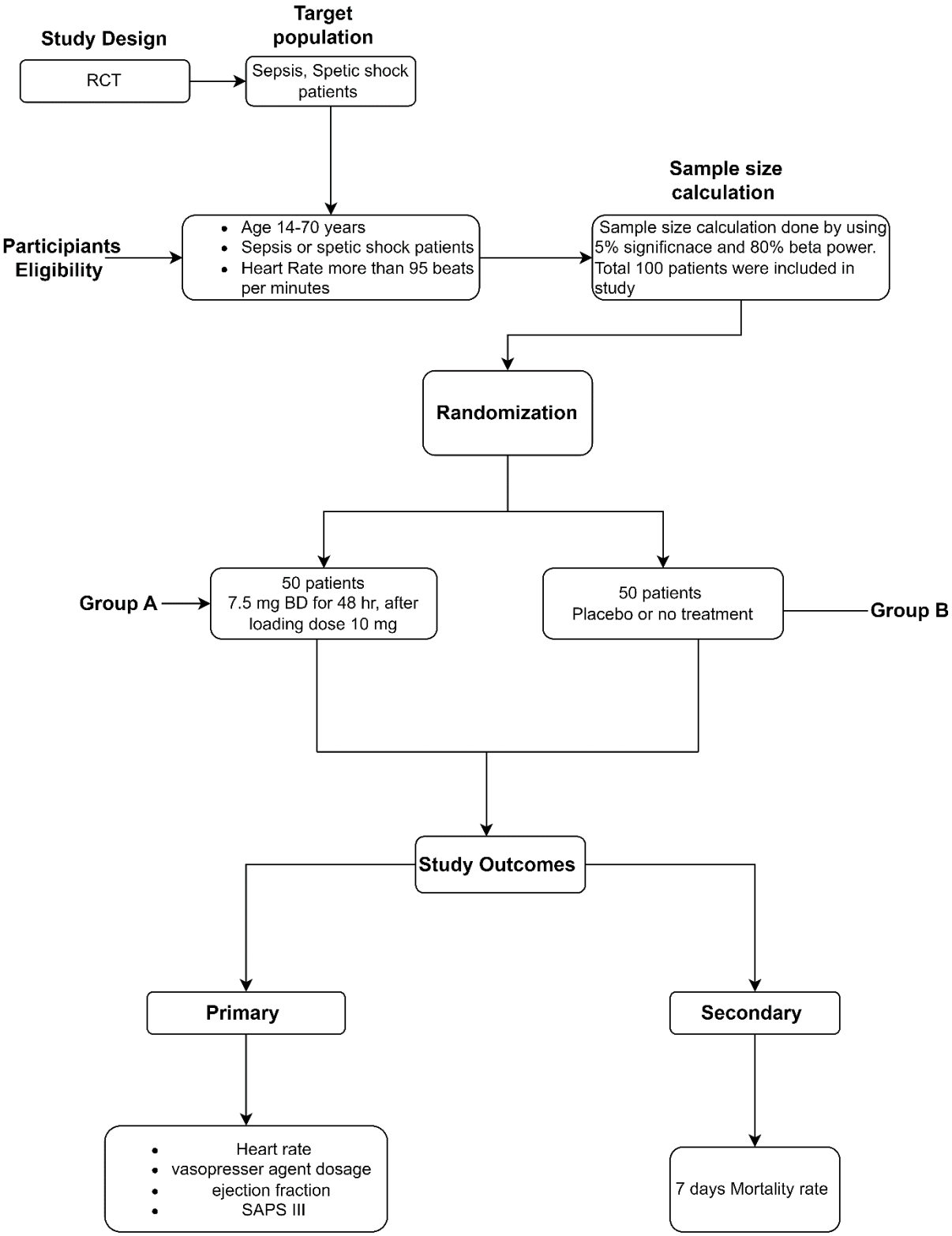


**Figure 1. Methodological process**

# 3. Results

## 3.1. Study Sample

A total of 100 patients were recruited for this study. The patients were randomly allocated to two groups: Group A (Ivabradine group: n = 50) and Group B (control group: n = 50).

The overall mean age of the patients was 32.49 ± 16.22 years. The mean age of the patients in Group B was significantly greater than that of those in Group A (p = 0.019). There were a total of 56 (56%) male and 44 (44%) female patients in the study. The gender distribution was matched at the baseline in Table 1.

**Table 1. Mean Ages and gender for Groups A and B**

| | **Group A** | **Group B** | **P-value** |
|---|---|---|---|
| Age (years) | 28.7 ± 12.66 | 36.28 ± 18.49 | 0.019 |
| **Group** | **Male** | **Female** | |
| Ivabradine | 29 (51.8%) | 21 (47.7%) | |
| Control | 27 (48.2%) | 23 (52.3%) | 0.687 |
| **Total** | 56 (100%) | 44 (100%) | |

## 3.2. Primary Diagnosis

In the process of determining the primary diagnosis, among the total sample size of 100 patients, 12% were diagnosed with epilepsy, followed by tetanus at 11%. The least prevalent diagnoses among the participants were ARDS (acute respiratory distress syndrome) and ARF (Acute Renal Failure). The patients exhibited a diverse array of primary diagnoses, which have been detailed in Table 2 to illustrate their frequency distribution.

**Table 2. Primary diagnosis of the participants**

| **Diagnosis** | **Frequency (%)** |
|---|---|
| ARDS | 2 (2) |
| ARF or CRF | 3 (3) |
| ARF and Snake Bite | 5 (5) |
| Asthma | 3 (3) |
| CAP | 9 (9) |
| Carbon Monoxide Poisoning | 3 (3) |
| DIC/Septic Shock | 5 (5) |
| DKA | 2 (2) |
| Encephalitis | 7 (7) |
| Epilepsy | 12 (12) |
| Gastroenteritis | 7 (7) |
| GBS | 2 (2) |
| Post-enteric fever gut perforation | 2 (2) |
| HHS | 5 (5) |
| Myasthenia Gravis | 3 (3) |
| NMS | 5 (5) |
| Opioid Poisoning | 4 (4) |
| PAH with ILD | 4 (4) |
| Purpureal Sepsis | 3 (3) |
| TBM | 3 (3) |
| Tetanus | 11 (11) |
| **Total** | **100 (100)** |

Note: ARDS = acute respiratory distress syndrome; ARF = Acute Renal Failure; CRF = Chronic Renal Failure; CAP = Community Acquired Pneumonia; DIC = Disseminated Intravascular Coagulation; DKA = Diabetic Ketoacidosis; GBS = Guillain-Barré Syndrome; HHS = Hyperosmolar Hyperglycemic State; NMS = Neuroleptic Malignant Syndrome; PAH = Pulmonary Arterial Hypertension; ILD = Interstitial Lung Disease; TBM Tubercular Meningitis)

### 3.3. Type of Infection

Table 3 presents a comprehensive overview of the types of infections observed in both study groups. Ventilator-associated pneumonia (VAP) emerged as the most prevalent infection, with a total of 60 cases, followed by Catheter-Related Bloodstream infection (CRBSI) with 42 cases. Additionally, Community Acquired Pneumonia (CAP) was identified in 12 cases, while liver abscesses were found in 4 cases.

**Table 3. Types of Infection in Both Groups (n = 100; CAP = Community Acquired Pneumonia; CRBSI = Catheter-Related Bloodstream Infection; VAP = Ventilator Associated Pneumonia)**

| Type of Infection | Group A | Group B | Total |
|---|---|---|---|
| CAP | 2 (4%) | 5 (10%) | 7 (7%) |
| CAP & CRBSI | 2 (4%) | 3 (6%) | 5 (5%) |
| CRBSI | 14 (28%) | 8 (16%) | 22 (22%) |
| CRBSI & VAP | 6 (12%) | 9 (18%) | 15 (15%) |
| VAP | 22 (44%) | 23 (46%) | 45 (45%) |
| Liver Abscess | 2 (4%) | 2 (4%) | 4 (4%) |
| None | 2 (4%) | 0 (0%) | 2 (2%) |
| **Total** | **50** | **50** | **100** |

### 3.4. SAPS III

The overall mean SAPS III score was 54.28 + 17.34. There was no significant difference in the SAPS III scores between the two groups ($p = 0.291$).

### 3.5. Heart Rate

The heart rate was recorded at baseline. Thereafter, the heart rate was measured at 12, 24, 48, 72, 96, and 120 hours. The heart rates at these different time intervals have been shown in Table 4. The mean heart rate of the patients in Group A were significantly greater at baseline ($p = 0.001$), 44 hours ($p = 0.43$), 72 hours ($p = 0.001$) and 96 hours ($p < 0.001$).

**Table 4. Mean Heart Rates for Groups A and B (n = 100)**

| Timing | Group A | Group B | Total | P-value |
|---|---|---|---|---|
| Baseline | 126.62 ± 12.30 | 118.94 ± 10.62 | 122.78 ± 10.07 | **0.001** |
| 12 Hours | 121.74 ± 9.45 | 119.3 ± 10.01 | 120.52 ± 9.76 | 0.213 |
| 24 Hours | 119.66 ± 10.93 | 119.4 ± 11.11 | 119.53 ± 10.97 | 0.906 |
| 48 Hours | 114.68 ± 9.89 | 119.52 ± 13.39 | 117.1 ± 11.96 | **0.043** |
| 72 Hours | 110.18 ± 9.15 | 118.16 ± 13.86 | 114.17 ± 12.35 | **0.001** |
| 96 Hours | 106.92 ± 10.53 | 106.92 ± 15.78 | 111.92 ± 14.26 | **< 0.001** |
| 120 Hours | 103.42 ± 11.47 | 110.02 ± 30.96 | 106.72 ± 23.46 | 0.162 |
| **Baseline and Post-intervention mean MAP values for Groups A and B (n = 100)** | | | | |
| Baseline | 66.06 ± 6.77 | 65.62 ± 2.93 | 65.84 ± 5.19 | NA |
| Post-Intervention | 67.74 ± 6.73 | 66.16 ± 4.56 | 66.95 ± 5.77 | NA |

The change in heart rate was analyzed at 24, 28, and 120 hours. As compared to baseline levels, the mean heart rate for Group A increased, while that for Group B significantly decreased. A seminal trend and significant difference in heart rates between the two groups was observed at 48 and 120 hours as well (see Figure 2).

The mean change in heart rate from baseline to 24, 48, and 120 hours was compared between the two groups. As shown in Table 4, the mean reduction in heart rate for Group A was significantly greater than that for Group B at 24 ($p < 0.001$), 48 ($p < 0.001$) and 120 hours ($p = 0.002$).

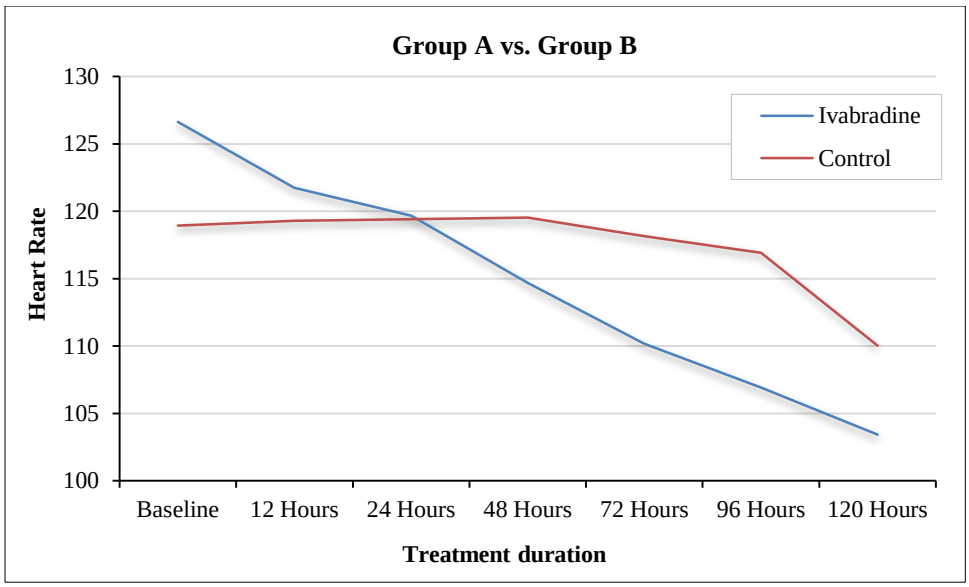


**Figure 2. Heart rates at different time intervals for groups A and B**

### 3.6. Mean Arterial Pressure

Baseline and post-intervention (120 hours) measurements for mean arterial pressure (MAP) were taken (Table 4). The mean reduction in MAP for Group A patients was found to be significantly greater than that for Group B patients ($p = 0.022$).

### 3.7. Norepinephrine Dosage

Baseline and post-intervention (120 hours) measurements for norepinephrine dosage (NE dosage) were taken (Table 4). There was no difference in the mean change in NE dosage between the two groups ($p = 0.106$).

### 3.8. Ejection Fraction

Baseline and post-intervention (120 hours) measurements for ejection fraction (EF) were taken. The mean increase in EF for Group A patients was found to be significantly greater than that for Group B patients ($p = 0.009$).

### 3.9. Mortality

A total of 22 (44%) patients died in group A, while 24 (48%) patients died in group B. There was no significant difference in the frequency distribution of mortality between the two groups ($p = 0.688$).

## 4. Discussion

In this study, we evaluated the effects of ivabradine vs. placebo in patients with sepsis. Sepsis is a potentially life-threatening condition affecting millions of individuals worldwide. Persistent tachycardia seen in patients with sepsis can progress to multiple organ dysfunction syndrome (MODS) and have adverse outcomes for the patient. In order to improve the survival of these patients, a reduction in heart rate may be a useful measure [20].

Moreover, critically ill patients are susceptible to stress-induced cardiac dysfunction, which causes an increase in sympathetic activity, which in turn leads to tachycardia. However, it might be difficult to lower the HR in such patients, as the use of drugs like beta-blockers, which are usually used to reduce the heart rate, also has inotropic effects that increase heart contractility [21]. Ivabradine is a negative chronotropic drug and may be used in patients with sepsis to effectively manage tachycardia [22]. Moreover, a study found 55.6% of patients in the Ivabradine group reported a reduction in HR of at least 10 bpm compared to 38.2% in the control group [23].

In 2017, Bocchi et al.'s study was set up to be a randomized, placebo-controlled experiment with a prospective design. Patients with symptomatic systolic HF from Chagas heart disease were recruited and randomly assigned to receive either ivabradine or a placebo. The progress of patients in both groups was tracked throughout time. The effects of ivabradine on exercise capacity, heart failure symptoms, and cardiac function were the key measures of success in this trial. The influence of ivabradine on secondary outcomes, such as cardiovascular events including hospitalization rates, and side effects, was also evaluated [24]. The objective of the Bedet et al. study from 2020 was to evaluate and contrast the effects of ivabradine, beta-blockers, and placebo on heart rate regulation in mice during experimental sepsis. Sepsis is a potentially fatal illness brought on by an extreme immune response to an infection, and its effects on the circulatory system are key to understanding its pathophysiology. The study was designed to shed light on the potential advantages of ivabradine and beta-blockers as therapeutic interventions for controlling heart rate changes in sepsis,

which may have implications for the creation of novel therapeutic approaches for this serious medical condition [22]. In a similar study by Bohm et al. conducted in 2015, a significant reduction in HR was reported with ivabradine (343 bpm) as compared to placebo (425 bpm) in mice with experimental sepsis [25].

Fox et al. (2014) conducted the SIGNIFY trial to investigate the mortality rates associated with cardiovascular causes or non-fatal myocardial infarction (MI) in patients with stable coronary artery disease but without chronic heart failure. However, the study did not reveal any statistically significant difference in the combined mortality rate attributed to cardiovascular causes or non-fatal MI between the two groups under investigation [26].

Swedberg et al.'s (2010) SHIFT trial on the effects of ivabradine on people with chronic heart failure showed that the HR was 15 bpm lower than it was at the start (80 bpm). A significant reduction in HR ($p<0.001$) was observed with ivabradine [27]. However, no significant effects were seen in arterial blood pressure, except 15 minutes after administration of the drug, when a clinically insignificant, mild decrease in MAP was observed. A study reported a significant reduction in HR ($p = 0.0001$) with ivabradine as compared to saline alone [27].

De Santis et al. (2014) studied three patients receiving ivabradine who developed sepsis-related MODS after cardiac surgery, and reported that hemodynamic improvement resulted in a reduction in the dose of norepinephrine. This was explained by the ability of the drug to reduce HR with a concomitant increase in stroke volume index, end diastolic volume index, and central venous oxygen saturation. The improvement in hemodynamic parameters led to a consistent reduction in serum lactate levels and reduced nor epinephrine dose. Whereas a study by Bedet et al. reported a significantly reduced mortality with Ivabradine (25%) as compared to placebo (50%) 30 hours after treatment [22]. However, the results didn't persist long, and at 60 hours, mortality with ivabradine (75%) increased ($p=0.224$) as compared to placebo (70%) [28].

There are certain limitations to our study, such as the chance of bias in patient selection and treatment allocation, the small sample size, and the absence of a double-blind methodology. Additionally, the study evaluated ivabradine's potential side effects and safety in patients; however, the management was more challenging. The clinical ramifications of this study showed that ivabradine was helpful in regulating heart rate in patients with sepsis and septic shock. This finding may have consequences for the management of these patients and may improve outcomes. To validate these effects and determine the ideal dosage and length of treatment, additional research may be required. Nevertheless, the study's conclusions should be regarded cautiously.

## 5. Conclusion

Patients receiving ivabradine for the treatment of sepsis demonstrate a notable reduction in heart rate compared to those administered a placebo. Additionally, ivabradine exerts a positive impact on cardiac function, as evidenced by a significant increase in ejection fraction and mean arterial pressure. These changes indicate an enhanced ability of the heart to efficiently pump blood throughout the body, reflecting improved performance. Moreover, ivabradine usage leads to a decreased requirement for vasopressors, such as epinephrine, in achieving the desired therapeutic effect, streamlining medication administration for patients. It is essential to highlight, however, that despite these favorable effects, ivabradine does not correlate with an overall reduction in mortality rates. This point holds paramount importance and deserves utmost attention. As a result of its demonstrated efficacy, ivabradine merits inclusion among the therapeutic options recommended in the guidelines for managing patients in the intensive care unit (ICU). Strong support exists for its integration into these guidelines to ensure optimal treatment outcomes for critically ill patients.

## 6. Declarations

### 6.1. Author Contributions

Conceptualization, S.M.M.A. and M.I.M.; methodology, S.M.M.A.; software, T.A.; validation, S.S.K., T.M.U.P., and R.M.S.; formal analysis, F.R.; investigation, S.M.M.A.; resources, M.I.M.; data curation, A.B.; writing—original draft preparation, S.M.M.A.; writing—review and editing, T.A. and M.K.; visualization, S.M.G.; supervision, M.I.M.; project administration, M.I.M. All authors have read and agreed to the published version of the manuscript.

### 6.2. Data Availability Statement

The data presented in this study are available in the article.

### 6.3. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### 6.4. Ethical Approval and Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shaheed Zuilfiqar Ali Bhutto Medical University Islamabad (1-1/2015/ERB/SZABMU; date: 26 July 2017).

### 6.5. Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

### 6.6. Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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