Original Article

Ivabradine In Patients With Systemic Inflammatory Response Syndrome

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Abstract

Introduction: ivabraddine is a pure heart rate lowering medication that its usage is beneficial in SIRS and MODS as it can reduce heart rate and decrease oxygen consumption especially at low ejection fraction where other medications cannot undergo their potential cardioprotective effect**. Aim of work**: The aim of this case study was to report the use of Ivabradine in patients who developed SIRS and compare this group with patients who developed SIRS without Ivabradine use for incidence of changes in systolic and diastolic indices, ejection fraction EF and cardiac index CI and effects on hemodynamics, organ perfusion parameters, and outcome of SIRS and MODS. **Patients and methods:** Patients who presented to emergency department with SIRS and admitted to ICU. The study population will include 40 patients who developed SIRS and admitted to ICU. A total of 40 patients were divided into two groups: **Group I:** SIRS patients with ivabradine treatment. **Group II:** SIRS patients without Ivabradine treatment. **Results**; Comparative study between the 2 groups revealed, highly significant increase in follow up SvO2, EF and CI, at end of Ivabradine treatment, compared to control group without Ivabradine treatment ($p < 0.05$ respectively). **Conclusion:** By comparative study between two groups of sepsis there was a significant improvement in cardiac indices in Ivabradine group at the end of the study (high cardiac index and ejection fraction), In addition to improvement of petfusion parameters.

Keywords: ivabradine, SIRS, myocardial dysfunction

INTRODUCTION

Severe sepsis is a leading cause of morbidity and mortality universally. Sepsis almost leads to multiple organ dysfunction syndromes (MODS) that is represented by an acute functional impairment of two or more organs as a result without management survival cannot be achieved. [1]

The term SIRS might not shock as a subset of sepsis in which ongoing circulatory and cellular metabolism abnormalities are evident enough to give rise in mortality incidence. Beside assumed definitions, clinical guidelines suggested by Sepsis-3 recommend the use of a total sequential organ failure assessment (SOFA) score more or equal to two in patients with proven infection to identify a patient with sepsis. Indicates the need to identify sepsis patient prior to available laboratory test values required for calculation of SOFA, a new feasible and no costly easily assessed bedside clinical score, termed quick SOFA (qSOFA), was introduced in the Sepsis-3. The qSOFA score calculates from zero to three points pointing to each of the clinical variables, respiratory rate (RR) 22 breaths/min, Glasgow Coma Scale (GCS) < 15 and systolic blood pressure 100 mm Hg. [2]

Cardiovascular dysfunction in sepsis or sepsis induced myocardial dysfunction (SIMD) SIMD has been identified as a reversible biventricular decrease in EF, with ventricular dilation and less fluid resuscitation and catecholamines responsiveness. However, it is too simplistic as left ventricular EF does not reflect intrinsic myocardial contractile function. In fact it is a load-dependent index that collectively determined by the coupling between left ventricular afterload and contractility. [3]

MODS Patients almost suffer an increased heart rate (HR) that accompanies an autonomic dysfunction in addition to depressed parasympathetic drive of the heart. An elevated heart rate was found to increase the incidence of major cardiac events in patients who are critically ill. [4]

Moreover, the elevated heart rate in MODS early phase was found to be an independent predictor of increased 28-day mortality. As the currently available specific therapies for the treatment of MODS show only less therapeutic benefits in relation to its high incidence and mortality, there is an urgent need for advanced strategies and regimes to improve the prognosis of MODS. [5]

Ivabradine is only heart rate-lowering medication that undergoing its action specifically on the sinoatrial node by selectively inhibiting the hyperpolarization-activated cyclic nucleotide (HCN) channel of cardiac pacemaker cells by entering and binding to a position in the channel pore from the intracellular side without affecting the other cardiac ionic currents. Two very important prospective randomized trials have showed benefits derived from Ivabradine administration in patients with stable coronary artery syndrome and in chronic heart failure patients. [6]

In MODS beta-blockers had been tried to reduce mortality rates. However, negative inotropic effects of beta-blockers herald its usage in the many cases. So, Ivabradine may be considered as safe alternative therapeutic approach to reduce heart rate. As it is a pure heart rate lowering drug that selectively suppresses If. Ivabradine blocks pacemaker channels in a use-dependent way being more effective at higher heart rate while its action decreases during bradycardia. [7]

A significant heart rate reduction in patients with catecholamine induced postoperative tachycardia after high-risk cardiac surgery treated with Ivabradine was previously reported. [8]

PATIENTS AND METHODS

The aim of this double-blind case study was to report the use of Ivabradine in patients who developed SIRS and compare this group with patients who developed SIRS without Ivabradine use for incidence of changes in systolic and diastolic indices, ejection fraction EF and cardiac index CI and effects on hemodynamics, organ perfusion parameters, and outcome of SIRS and MODS.

Patients who presented to emergency department with SIRS and admitted to ICU. The study population will include 40 patients who developed SIRS and admitted to ICU.

A total of 40 patients were divided into two groups: **Group I:** SIRS patients with ivabradine treatment. **Group II:** SIRS patients without Ivabradine treatment

Inclusion criteria: Eligible patients aged ≥18 years and presented with suspected SIRS. Patients were evaluated in the emergency department and admitted to ICU where confirmed the primary diagnosis according to the following criteria (two of the following): Temperature: >38C^{o} or < 36 C^{o}, heart rate: > 90 BPM, respiratory rate > 20, Pco2< 32 mmHg, WBCs > 11000 OR < 4000/MM^{3} with >10% immature bands and suspected source of sepsis: (e.g. blood-stream, chest and pelviabdominal sepsis). [9]

Exclusion criteria: Patients who already have history of organ dysfunction, patients developed hepatic failure CHILD C, patients with bradycardia (HR<60 BPM), patients with NPO (nothing per oris), patients of non-sinus rhythm and patients presented with acute coronary syndrome and sepsis on admission.

Methods:

All patients subjected to:

Laboratory and hemodynamic parameters were measured for patients upon admission to the emergency department and enrollment in study included: Heart rate, systolic and diastolic arterial pressure, body temperature, respiratory rate, arterial blood gases, CBC, liver and kidney functions, serum Electrolytes, coagulation parameters and C-reactive protein (CRP).

Within 24 hours before Ivabradine treatment, echocardiography and chest X-ray were carried out. Considering Ivabradine dosage 5mg B.i.D.

In addition to conventional history inquiry, BMI, physical examination, and collection of relevant laboratory and imaging examination data.

Initial vasoactive medication for haemodynamic support was norepinephrine (0.05-0.1 mcg/kg/min).

Follow up parameters: Echocardiographic parameters: LVEDD, LVESD, EF, left atrial diameter, CI (cardiac index) on day 0 and on follow up after 2 days. **Laboratory data:** To confirm diagnosis and daily follow up. **Organ perfusion parameters:** SVO2 daily/ serum lactate daily. **Inflammatory parameters:** WBC count, and immature bands, CRP daily.

Outcomes: Mortality rate**,** morbidity**,** systolic and diastolic indices, EF and CI **and** hemodynamic parameters, and organ perfusion parameters

Possible risk and ethical committee approval: No risk is added as the drug use will not be used if contraindicated **and** the study subjected to ethical committee for approval and it was approved.

RESULTS

Table 1: Comparison between the 2 groups as regards basic clinical data using Student's t and Chi square tests:

Variable		Ivabradine group (20)	No Ivabradine group (20)	Student's t test
		Mean ± SD	Mean ± SD	P value
Age (years)		48.55 ± 16.96	50.85 ± 16.26	= 0.664
BMI		29.64 ± 4.39	30.62 ± 4.56	= 0.491
HR (beat/min)		115.7 ± 9.2	115.3 ± 7.5	= 0.896
MAP (mmHg)		72.6 ± 5.7	71.8 ± 5.6	= 0.639
Temperature (^{0})		38 ± 0.62	37.9 ± 0.7	= 0.512
RR (breath/min)		24.4 ± 3.7	23.7 ± 2.99	= 0.515
Variable		Ivabradine group (20)	No Ivabradine group (20)	Chi square test
				P value
Gender	Female Male	11 (55%) 9 (45%)	5 (25%) 15 (75%)	= 0.0559
DM	+ve	12 (60%)	11 (55%)	= 0.7521
HTN	+ve	9 (45%)	7 (35%)	= 0.5239
IHD	+ve	10 (50%)	7 (35%)	= 0.3434

* Percentage of Column Total

Comparative study between the 2 groups revealed non-significant difference as regards all basic clinical data (p > 0.05).

Table 2: Comparison between the 2 groups as regards baseline laboratory data using Student's t test:

Variable	Ivabradine group (20)	No Ivabradine group (20)	Student's t test
	Mean ± SD	Mean ± SD	P value
Ph	7.25 ± 0.067	0 ± 0	= 0.568
SvO2 (%)	50.9 ± 7.34	53.9 ± 5.75	= 0.159
HCO3 (mEq/l)	18.5 ± 2.8	18.75 ± 2.38	= 0.763
Hb (g/dL)	9.5 ± 1.3	9.56 ± 1.28	= 0.876
PLS (10^3/µL)	141.1 ± 54.9	129.9 ± 36.7	= 0.455

TLC (10^3/µL)	17.91 ± 4.22	17.95 ± 4.21	= 0.973
AST (U/L)	153.45 ± 91.3	109.9 ± 93.4	= 0.145
ALT (U/L)	83.4 ± 47	71 ± 41.4	= 0.382
Creat. (mg/dL)	1.7 ± 0.66	1.5 ± 0.42	= 0.241
Na (mEq/l)	134.4 ± 8.2	131 ± 6.6	= 0.158
K (mEq/l)	4 ± 0.87	3.86 ± 0.88	= 0.477
INR	1.51 ± 0.63	1.39 ± 0.39	= 0.479
Lactate (mg/dl)	7.08 ± 3.46	6.64 ± 2.06	= 0.628
CRP (mg/dl)	85.6 ± 38.4	96.4 ± 40.05	= 0.390

Comparative study between the 2 groups revealed non-significant difference as regards all baseline laboratory data ($p > 0.05$).

Table 3: Comparison between the 2 groups as regards baseline echocardiographic data using Student's t test:

Variable	Ivabradine group (20)	No Ivabradine group (20)	Student's t test
	Mean ± SD	Mean ± SD	P value
LVEDD (cm)	53.25 ± 6.86	49.8 ± 4.69	= 0.071
LVESD (cm)	41.1 ± 6.23	38.15 ± 4.4	= 0.092
EF (%)	0.45 ± 0.04	0.46 ± 0.04	= 0.476
LAD (cm)	3.82 ± 0.38	4.04 ± 0.35	= 0.074
CI (L/min/m2)	2.96 ± 0.33	3.01 ± 0.32	= 0.506

Comparative study between the 2 groups revealed non-significant difference as regards all baseline echocardiographic data ($p > 0.05$).

Table 4: Comparison between the 2 groups as regards follow up (48-h) data using Student's t test:

Variable		Ivabradine group (20)	No Ivabradine group (20)	Student's t test
		Mean ± SD	Mean ± SD	P value
Laboratory	**SvO2** (%)	53.25 ± 7.06	55 ± 6.36	= 0.416
	TLC (10^3/µL)	15.96 ± 3.8	16.49 ± 3.82	= 0.663
	Lactate (mg/dl)	5.91 ± 3.44	5.54 ± 1.9	= 0.672
	CRP (mg/dl)	77 ± 33.1	83 ± 40.2	= 0.610
Echo	**LVEDD** (cm)	53.7 ± 7	50.2 ± 4.6	= 0.077
	LVESD (cm)	39.9 ± 5.62	37.5 ± 4	= 0.130
	EF (%)	0.47 ± 0.03	0.47 ± 0.4	= 0.818
	LAD (cm)	3.82 ± 0.38	4.04 ± 0.35	= 0.074
	CI (L/min/m2)	3.02 ± 0.33	3.03 ± 0.35	= 0.499

Comparative study between the 2 groups revealed non-significant difference as regards follow up (48-h) data ($p > 0.05$).

Table 5: Comparison between the 2 groups as regards follow up (end of ttt) data using Student's t test:

Variable		Ivabradine group (20)	No Ivabradine group (20)	Student's t test
		Mean ± SD	Mean ± SD	P value
Laboratory	**SvO2** (%)	64.2 ± 7.6	56.8 ± 4.67	= 0.001**
	TLC (10^3/µL)	12.19 ± 2.5	12.49 ± 2.73	= 0.720
	Lactate (mg/dl)	2.46 ± 0.88	3.37 ± 1.23	= 0.01**

	CRP (mg/dl)	41.6 ± 23.5	47.9 ± 28.3	= 0.449
Echo	**LVEDD** (cm)	53.8 ± 6.9	50.3 ± 4.6	= 0.072
	LVESD (cm)	37 ± 9.48	37 ± 3.92	= 1.000
	EF (%)	0.51 ± 0.03	0.48 ± 0.04	< 0.001**
	LAD (cm)	3.81 ± 0.35	3.98 ± 0.36	= 0.129
	CI (L/min/m2)	3.28 ± 0.39	3.05 ± 0.39	= 0.029*

Comparative study between the 2 groups revealed, highly significant increase in follow up SvO2, EF and CI, at end of Ivabradine treatment, compared to control group without Ivabradine treatment ($p < 0.05$ respectively). Comparative study between the 2 groups revealed, highly significant decrease in follow up lactate at end of Ivabradine treatment, compared to control group without Ivabradine treatment ($p = 0.01$). Comparative study between the 2 groups revealed non-significant difference as regards follow up (end of ttt) TLC, CRP, LVEDD, LVESD and LAD ($p > 0.05$).

Table 6: Comparison between the 2 groups as regards mortality rate using Chi square test:

Variable		Ivabradine group (20)	No Ivabradine group (20)	Chi square test
				P value
Mortality rate	+ve	2 (10%)	8 (40%)	= 0.03*
LOS (days)		16 ± 3.6	14.2 ± 5.3	= 0.208
MV period (days)		4.1 ± 1.97	4.6 ± 2.4	= 0.475
Weaning of vasoactive drugs		18 (90%)	11 (55%)	= 0.014*

* Percentage of Column Total.

Comparative study between the 2 groups revealed, significant increase in mortality, in "No Ivabradine group", compared to Ivabradine group ($p = 0.03$). Comparative study between the 2 groups revealed, significant increase in weaning of vasoactive drugs, in "No Ivabradine group", compared to Ivabradine group ($p = 0.014$). Comparative study between the 2 groups revealed, non-significant difference in LOS and MV period between the 2 groups ($p > 0.05$).
The 2 groups showed marked increase CI (especially in Ivabradine treated group); during the serial measurements.

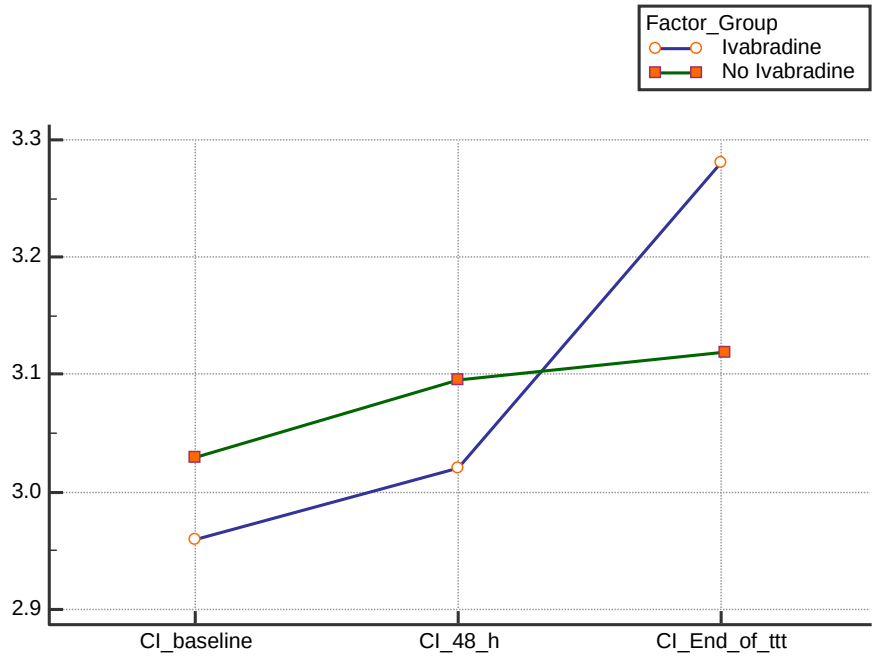

Figure 1: Comparison between the 2 groups of patients regarding serial CI assessments

Correlation studies between **mortality outcome**; and its **relative independent predictors (basic clinical, laboratory, echocardiographic and treatment variables)** will be conducted with logistic regression analysis and ROC curve analysis (as suitable).

Table 7: Logistic regression model for the Factors affecting mortality occurrence using Forward method:

Predictor Factor	Coefficient	Std. Error	P value
(Constant)	2.09722		
RR	0.61646	0.28007	0.027*
CI	-5.75819	2.34924	0.014*
Ivabradine usage	-5.36395	2.40560	0.025*

--- excluded from the model if (p value > 0.1).

Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the increase in baseline RR; had an independent effect on increasing the probability of mortality occurrence; with significant statistical difference (p = 0.027). Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the decrease in baseline CI, and decreased Ivabradine usage; had an independent effect on increasing the probability of mortality occurrence; with significant statistical difference (p < 0.05 respectively).

DISCUSSION

Mortality due to sepsis induced myocardiac dysfunction has been encountered in critically ill patients where an increase in heart rate may act as single independent risk factor. Patients with lower heart rate in the early phase of MODS and SIRS have favorable survival rates than those with higher elevated rate. [10]

Ivabradine is a heart rate-lowering medication that acts specifically on the sinoatrial node by selectively inhibiting the hyperpolarization-activated cyclic nucleotide (HCN) channel of myocardiac pacemaker cells by entering and binding to a position in the channel pore from the intracellular side without affecting the other myocardiac ionic currents. Two remarkable prospective randomized trials have showed benifits derived from Ivabradine usage in patients with stable coronary artery syndrome and in those suffering chronic heart failure [6]

This was a prospective double-blind case control study in critical care department; Cairo University will be conducted on 40 patients with SIRS; to assess the use of Ivabradine in patients who developed SIRS and compare this group with patients in SIRS without Ivabradine usage.

The study population included 40 patients who developed SIRS and admitted to ICU.

Patients were divided into two groups: Group I: SIRS patients with Ivabradine treatment and group II: SIRS patient without Ivabradine treatment.

Regarding base line data (table 1), we found that the mean age of all patients was (49.7 ± 16.4) years. Regarding gender of the patients, the majority (60%) of patients were males; while (40%) were females, which came in agreement with **Nuding et al. [8] and Bushman e al. [11]**

Jirak et al. [12] determined the inclusion criteria were as follows: (i) age >18 years; (ii) normal sinus rhythm; (iii) heart rate >75 bpm; (iv) left ventricular systolic hypofunction (LV-EF <50%); (v) dilated, ischemic, or hypertensive stable CHF >12 months.

The mortality rate was (25%), which came in agreement with (table 6) **Sathyamurthy and Newale, [13]**

Sathyamurthy and Newale, [13] dedicated that a pooled analysis of the results of both the SHIFT and the Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine administration in Coronary Disease and Left Ventricular Dysfunction patients (BEAUTIFUL) trial10 (n = 11,897) with a baseline HR of 70 bpm revealed mean HR at baseline

was 79.6 ± 9.2 bpm, and the mean EF was 30.3 ± 5.6% with no significant differences between both groups. There was a 13% relative risk reduction in CV mortality or hospitalization for HF ($p < 0.001$). Significant risk reduction was also observed for the composite outcomes of CV mortality, HF hospitalizations, or myocardial infarctions (MIs)

Comparative study between the 2 groups revealed non-significant difference as regards all baseline laboratory data ($p > 0.05$) (table 2), which came in agreement with [12]

Regarding follow up data, comparative study between the 2 groups revealed, highly significant increase in follow up SvO2, EF and CI, at end of Ivabradine treatment, compared to control group without Ivabradine usage ($p < 0.05$ respectively) (table 5), which came in agreement with **Wu et al. [14], Sathyamurthy and Newale, [13], Buschmann et al. [11]** and **Vincent, [15]**

Wu et al. [14] reported that, the primary outcome was the improvement of the EF, which was measured using the biplane Simpson's method on echocardiographic assessment. Initial echocardiographic evaluation was done 3 days prior to initiation of Ivabradine administration, and the follow up evaluation was carried out 2 weeks following the first Ivabradine usage [14]

Sathyamurthy and Newale, [13] reported that, in a randomized, double-blind, placebo-controlled study (n =116) among dilated cardiomyopathy children with stable chronic heart failure (CHF) and 12 months of follow-up, Ivabradine was significantly effective in achieving primary end point (70% vs 12%; odds ratio 17.24; $p < 0.0001$). There was a significant improvement in LVEF with Ivabradine as compared with placebo (13.5% vs. 6.9%; p=0.024)

Buschmann et al. [11] reported that, Sepsis with microcirculatory alterations and mitochondrial destruction lead to circulatory affection, and all these elements reduce cellular energy production. This is the origin of sepsis-induced myocardial dysfunction mediated by cytokines. This cycle was prohibited in survivors, so that the myocardium may in fact experience a hibernation-like nonfunctional condition whilst severe sepsis. To decrease myocardial oxygen consumption, β-blocker Ivabradin and insulin are recommended as therapy strategy.

Vincent reported that, fixed of oral doses Ivabradine administeration (Starting dose 10mg followed by a maintenance dose of 5 mg every 12 h) for 18 h in three septic shock patients with multiple organ dysfunction syndrome. Heart rate (mean difference -27.6) and end-diastolic volume index, stroke volume index, MAP and SvO2 increased which come in concordance with our study 15

Comparative study between the 2 groups revealed, highly significant decrease in follow up lactate at end of Ivabradine treatment, compared to control group without Ivabradine treatment ($p = 0.01$), which came in agreement with **Wu et al. [14]** and **Vincent, [15]**

Vincent reported that, Ivabradine usage oral fixed doses (starting dose 10mg followed by a maintenance dose of 5 mg every 12 h) for 18 h in three septic shock patients with multiple organ dysfunction syndromes. Heart rate (mean difference -27.6) pulmonary capillary wedge pressure and right atrial pressure did not change over time; arterial lactate concentrations decreased and norepinephrine requirements were reduced which come in agreement with our study (table 6). 15

Wei reported that, addition of Ivabradine induced a decrease in HR(rats) (controls: 425 bpm vs. controls + Ivabradine: 343 bpm ; p=0.0001) while having no effect on either MAP (controls: 80 mmHg [75-96] vs. controls + Ivabradine: 75 mmHg ; p>0.05), SV (controls: 127µl vs. controls + Ivabradine: 105µl ; p>0.05), or hyperlactatemia (controls: 2.4 mmol.l- 1 vs. controls + Ivabradine: 2.5 mmol.l-1; p>0.05) in which these results come in disagreement with our study 16

Regarding outcome data ,comparative study between the 2 groups revealed significant increase in mortality, in "No Ivabradine group", compared to Ivabradine group ($p = 0.03$) (table 6), which came in agreement with **Sathyamurthy and Newale 13**

We further analyzed and compared all 40 (paired) patients according to the serial (laboratory and Echo measurements); with entering a grouping factor **(Ivabradine or Not)**;

The 2 groups showed marked increase in SvO2 (especially in Ivabradine treated group); during the serial measurements, which came in agreement with **Vincent** and **Sathyamurthy and Newale 13, 15**

Sathyamurthy and Newale reported that, tacchycardia may provoke myocardial ischemia in CAD patients. HR reduction decreases myocardial oxygen consumption and thereby helps to keep its viability. Reduced HR also

lengthens diastolic perfusion time and coronary flow reserve. These impacts help to increase ischemic threshold and give beneficial effects in angina patients.so increase in svo2 13

The 2 groups showed marked decrease in lactate (especially in Ivabradine treated group); during the serial measurements, which came in agreement with **Vincent,** [15] and **Wu et al.** [14]

The 2 groups showed marked increase in EF (especially in Ivabradine treated group); during the serial measurements, which came in agreement with **Wu et al.** [14] and **Sathyamurthy and Newale,** [13]

The 2 groups showed marked increase in CI (especially in Ivabradine treated group); during the serial measurements (table5 and diagram 7), which came in disagreement with **Vincent,** [15]

Logistic regression analysis shows that; after applying (Forward method) and entering some predictor variables; the decrease in baseline CI, and decreased Ivabradine usage; had an independent effect on increasing the probability of mortality occurrence; with significant statistical difference ($p < 0.05$ respectively)(table 8), which came in agreement with **Sathyamurthy and Newale,** [13]

CONCLUSION

By comparative study between two groups of sepsis there was a significant improvement in cardiac indices in Ivabradine group at the end of the study (high cardiac index and ejection fraction). Improvement of cardiac indices in Ivabradine group had a significant impact on perfusion parameters as serum lactate and svo2 at end of follow up. The only independent factors that predict low mortality were respiratory rate, cardiac index and Ivabradine usage.

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List of abbreviations

BMI; body mass index
CBC; complete blood count
CHF; chronic heart failure
CI; cardiac index
CRP; C - reactive protein
FF; ejection fraction
GCS; galascow coma scale
HCN; hyperpolarization-activated cyclic nucleotide
HR; heart rate
LAD; left atrial diameter
LVEDD; left ventricular end diastolic diameter
LVESD; left ventricular end systolic diameter
LV; left ventricle
MODS; multiple organ dysfunction syndrome
NPO; nothing per oris
RR; respiratory rate
SIMD; sepsis induced myocardial dysfunction
SIRS; systemic inflammatory response syndrome
SOFA; sequential organ failure assessment