



Comparative Study between Ivabradine Versus Bisoprolol Effects for Heart Rate Control on Hemodynamics and Clinical Outcomes in Patients with Septic Shock

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Septic shock is associated with excessive sympathetic outflow, high plasma catecholamine levels, myocardial depression, vascular hypo-reactivity, and autonomic dysfunction. Typically, patients have a low resistance, high cardiac output circulation with tachycardia and arterial hypotension that may be poorly or even nonresponsive to exogenous catecholamine vasopressors. The aim of the present study was to compare the effect of ivabradine vs bisoprolol for heart rate control on the hemodynamics and clinical outcomes in patients with septic shock.

Methods: The study was carried out on 90 patients, aging from 18 to 60 years of both sex presented with septic shock in ICU. Patients were randomly classified into 3 equal groups each of 30 patients. Group I (Control group) received conventional therapy. Group II (Bisoprolol group) received conventional therapy plus bisoprolol 5 mg once daily & one placebo pill on 12 hrs interval via nasogastric tube for 7 days. Group III (Ivabradine group) received conventional therapy plus ivabradine 5 mg twice daily on 12 hrs interval via nasogastric tube for 7 days.

Results: Both bisoprolol and ivabradine effectively lowered heart rate in septic shock patients but

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ivabradine was more effective than bisoprolol. Both bisoprolol and ivabradine did not affect mean blood pressure, with ivabradine being more effective in maintaining blood pressure than bisoprolol. Noradrenaline dose was lower in ivabradine group in comparison with the other two groups. As regard to stroke volume & cardiac output, there was improvement in ivabradine group in comparison with bisoprolol and control groups. As regard to serum lactate level, there was improvement in ivabradine group in comparison with the other two groups. Both bisoprolol & ivabradine resulted in reduction in LOS & 28-day mortality with no significant difference between both groups.

Conclusions: Controlling heart rate in septic shock patients with either bisoprolol or ivabradine improves outcomes. Ivabradine is better than bisoprolol in maintaining hemodynamics and improving tissue perfusion parameters.

Keywords: Ivabradine; bisoprolol; hemodynamics; clinical outcomes; septic shock.

1. INTRODUCTION

Septic shock is associated with excessive sympathetic outflow, high plasma catecholamine levels, myocardial depression, vascular hypo-reactivity, and autonomic dysfunction [1-2]. Typically, patients have a low resistance, high cardiac output circulation with tachycardia and arterial hypotension that may be poorly or even nonresponsive to exogenous catecholamine vasopressors. Although norepinephrine is the current recommended mainstay of treatment for sepsis-related hypotension [3], excessive adrenergic stress has multiple adverse effects including direct myocardial damage [4].

There are many potential benefits of beta-blockers for acutely ill patients. This includes a decreased oxygen demand related to a decreased heart rate (HR) [5]. Beta-blocker drugs are widely used as HR lowering drugs. However, these agents have negative inotropic activity, which is inappropriate in hemodynamic instability. A selective HR-lowering agent such as bisoprolol could thus be of therapeutic value in this context [6].

Ivabradine is a pure HR-lowering drug that acts specifically on the sinoatrial node by selectively inhibiting the I_f (Funny current) current of cardiac pacemaker cells without affecting the other cardiac ionic currents [7].

Electrical Cardiometry (EC) is a device for non-invasive determination of stroke volume (SV), cardiac output (COP), and other hemodynamic parameters. EC has been validated against "gold standard" methods such as thermodilution and echocardiography [8-11].

The aim of the present study was to compare the effect of ivabradine vs bisoprolol for heart rate

control on the hemodynamics & clinical outcomes in patients with septic shock.

2. PATIENTS AND METHODS

This randomized controlled study was carried out on 90 patients, aging from 18 to 60 years, of both sex presented with septic shock and requiring nor-epinephrine to maintain mean arterial pressure (MAP) \geq 65 mm Hg in ICU at Tanta University Hospital, Egypt from December 2018 to June 2020.

Exclusion criteria were: patients receiving β -blocker or ivabradine therapy prior to selection and patients having pronounced diagnosed cardiac dysfunction (e.g. cardiomyopathy & severe valvular heart disease).

Sepsis was defined according to surviving sepsis campaign guidelines as infection with proof of organ dysfunction (as evidenced by Sequential Organ Failure Assessment [SOFA] score $>$ 2).

Patients were randomly classified to 3 equal groups each of 30 patients. They were randomized using a computer-generated random number table to receive conventional management only or with bisoprolol or ivabradine. Group allocation was done by a sealed opaque envelope technique containing the randomly selected number; the envelope was opened by another investigator who had no subsequent involvement in the study.

Group I: "Control group": Patients received conventional therapy for management of septic shock including fluid resuscitation, noradrenaline infusion, and hydrocortisone (50mg / 6 hrs for 7 days).

Group II: "Bisoprolol group": Patients received conventional therapy for management of septic

shock plus bisoprolol (Concor ® 5 mg Brand: Merck) in a dose of 5 mg tabs once daily via nasogastric tube for 7 days. The pill was crushed by the nurse and dissolved in 10 ml of water via NGT & another placebo pill was given at 12 hrs interval crushed and dissolved in 10 ml of water to assure blindness of the study.

Group III: "Ivabradine group": Patients received conventional therapy for management of septic shock plus ivabradine (Proclolan 5 mg Manufactured by: Les Laboratoires Servier Industrie - France. Packed by: servier egypt industries limited - A.R.E.) in a dose of 5 mg tabs twice daily every 12 hrs via nasogastric tube for 7 days. The pill was crushed by the nurse and dissolved in 10 ml of water via NGT.

All patients were sedated by midazolam and received mechanical ventilation using volume-controlled mode with target tidal volume of 6 ml/kg of predicted body weight. Nasogastric tube, arterial line & central line were inserted. EC was connected. Precautions needed to increase accuracy of measurement were applied e.g. cleaning the skin & making sure it is dry before placing the electrodes. Four electrodes were applied: First: approximately 5 cm above the base at the anterior aspect of the neck. Second: 5 cm below the first electrode at the base of the neck. Third: on the lower left thorax in line with xiphoid process at the level of anterior axillary line. Fourth: 5 cm below the 3rd electrode at the level of anterior axillary line. EC was connected to the sensor cable and patient's data were fed (gender - age – height – weight – blood pressure –HR– SpO₂ – Hb concentration).

2.1 Measurements and Monitoring

1. HR and MAP were recorded at baseline, then median of the values recorded at the end of day 1, 3,5&7 after initiation of therapy.
2. Dose of noradrenaline needed was recorded at baseline, then at the end of day 1, 3,5,&7 after initiation of therapy.
3. SV (using EC) was recorded at baseline, then median of the readings recorded at the end of day 1, 3,5&7 after initiation of therapy.
4. COP (using EC) was recorded at baseline, then median of the readings recorded at the end of day 1, 3,5&7 after initiation of therapy.
5. Serum lactate was recorded at baseline then at the end of day 1, 3,5&7 after initiation of therapy. Done automated on

Beckman Coulter analyser depending on colorimetric method using Lactate Beckman Coulter kit.

6. Length of ICU stay (LOS) & 28 days Mortality were recorded and compared in the three studied groups.

Primary outcome was the reduction of heart rate during period of therapy while the secondary outcomes were noradrenaline dosage reduction, improvement in hemodynamic measures e.g. increased SV & COP and improvement in tissue perfusion by reduction in level of serum lactate.

2.2 Justification of Sample Size

The sample size was calculated using Epi-Info software statistical package created by World Health organization and Center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation were as follows: 95% confidence limit, 80% power of the study and expected primary outcome in treatment groups 80 % compared to 20 % for control group. The sample size based on the previously mentioned criteria was found at N>27 for each study group.

2.3 Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables and all variables are parametric (normally distributed). Quantitative variables were expressed as mean and standard deviation (SD) and were compared using F test among the three groups with post hoc (LSD) test to compare each two groups. Comparison between two variables within the same group was compared by paired T test. Categorical variables (e.g. sex) were expressed as frequency and percentage, and were statistically analyzed by Chi-square test. A two-tailed P value ≤ 0.05 was considered statistically significant.

3. RESULTS

In this study 117 patients were assessed for eligibility; 22 patients did not meet the criteria and 5 patients' relatives refused to participate in the study. The remaining 90 patients were randomly allocated into three equal groups (30 patients in each one). During the period of the study, 7 patients died in group I, 5 patients died in group II & 1 patient died in group III. All

patients were followed-up and analyzed statistically.

Demographic data including: age, sex & BMI were comparable in the three groups ($P > 0.05$). Table 1.

There was no statistically significant difference in heart rate between group I & II at day 1 ($P_1 > 0.05$). At day 3, 5 & 7 heart rate was significantly lower in group II compared to group I; ($P_1 < 0.001$). Also, comparison between group I & III showed that heart rate was significantly lower at day 1, 3, 5 & 7 in group III compared to group I ($P_2 < 0.001$). Comparison between group II & III showed that heart rate was significantly lower in group III at day 1, 3, 5 & 7 after start of TTT ($P_3 < 0.001$). Fig. 1.

There was no statistically significant difference in MAP between group I & II at day 1, 3, 5 & 7 ($P_1 >$

0.05). Also, comparison between group I & III showed that MAP was significantly higher in group III compared to group I at day 1 ($P_2 < 0.05$) and at day 3, 5 & 7 ($P_2 < 0.001$). Comparison between group II & III showed that MAP was significantly higher in group III compared to group II at day 1 ($P_3 < 0.05$) and at day 3, 5 & 7 ($P_3 < 0.001$). Fig. 2.

There was no statistically significant difference in NA dose between group I & II at day 1 & 3 ($P_1 > 0.05$) while at day 5 & 7 NA dose was significantly lower in group II ($P_1 < 0.05$). While comparison between group I & III showed that NA dose was significantly lower in group III at day 1, 3, 5 & 7 compared to group I ($P_2 < 0.001$). Comparison between group II & III showed also that NA dose was significantly lower in group III at day 1, 3, 5 & 7 compared to group II ($p_3 < 0.001$). Fig. 3.

Table 1. Demographic data

		Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	P value
Age (years)	Mean ± SD	44.17 ± 8.84	47.07 ± 9.11	48.4 ± 10.29	0.223
	Range	22-59	20-60	23-60	
Sex	Male	16 (53%)	18 (60%)	13 (43%)	0.429
	Female	14 (47%)	12 (40%)	17 (57%)	
BMI (kg/m ²)	Mean ± SD	24.3 ± 3.57	23.87 ± 3.26	24.94 ± 3.13	0.471
	Range	19.2-29.8	19.2-29.6	19.2-29.8	

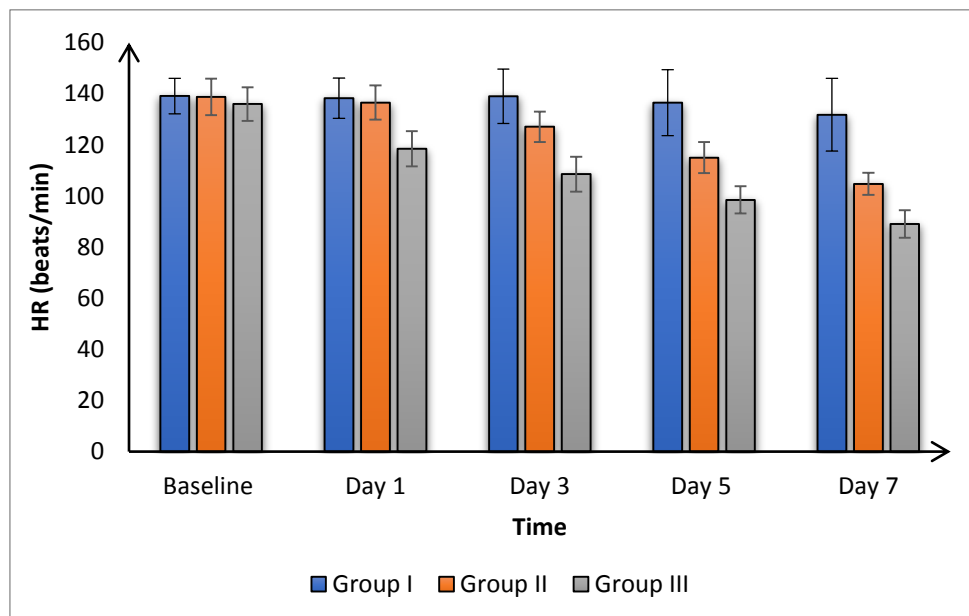


Fig. 1. Heart rate changes in all groups

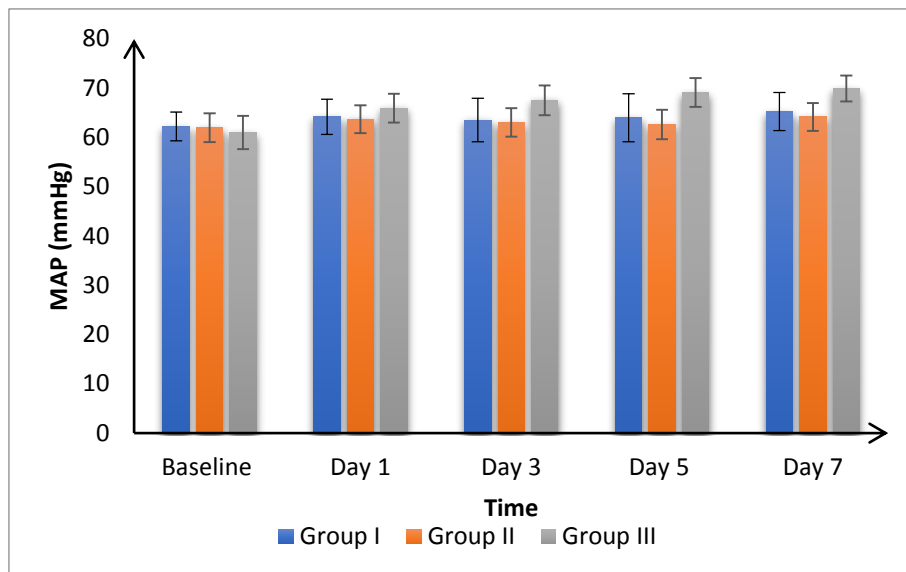


Fig. 2. Mean blood pressure changes in all groups

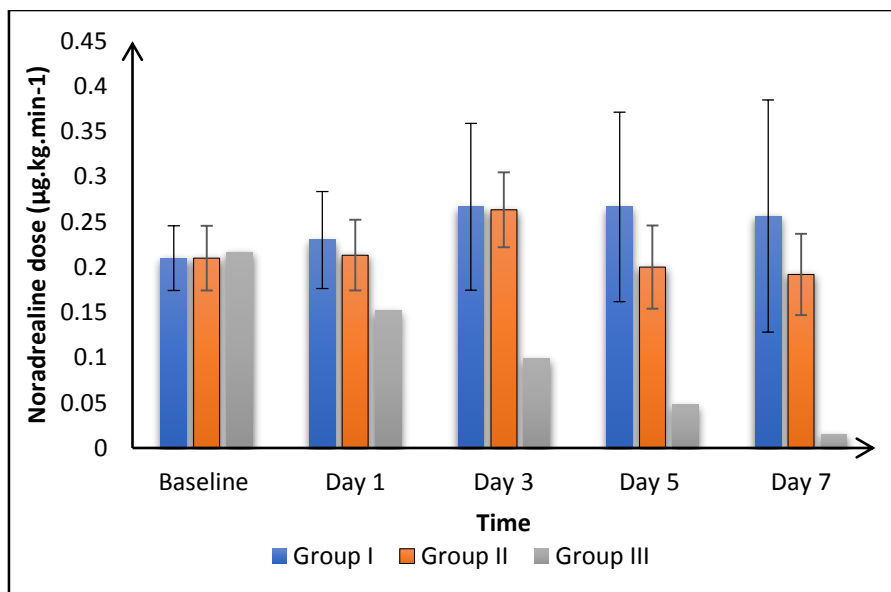


Fig. 3. NA dose comparison between all groups

Stroke volume improved in group III in comparison to the other two groups at day 3 ($P < 0.05$) and at day 5 & 7 ($P < 0.001$) Table 2.

Cardiac output improved in group III in comparison to the other two groups at day 3 ($P < 0.05$) and at day 5 & 7 ($P < 0.001$). Table 3.

There was no statistically significant difference in serum lactate level between group I & II at day 1, 3, 5 & 7 ($P_1 > 0.05$). While comparison between group I & III showed that serum lactate level significantly decreased in group III at day 1, 3, 5 & 7 compared to group I ($P_2 < 0.001$).

Comparison between group II & III showed also that serum lactate level was significantly lower in group III at day 1, 3, 5 & 7 compared to group II ($P_3 < 0.001$). Fig. 4.

Comparison between group I & group II showed that LOS decreased significantly in group II ($P_1 < 0.001$). Comparison between group I & group III showed that LOS decreased significantly in group III ($P_2 < 0.001$). While comparison between group II & group III showed that there was no statistically significant difference in LOS between group II & group III. ($P_3 > 0.05$). Table 4.

Table 2. Variation of stroke volume in all groups

		Baseline	Day 1	Day 3	Day 5	Day 7
Group I	Low (n.)	30	30	30	22	18
	Normal (n.)	0	0	0	5	5
Group II	Low (n.)	30	30	30	21	16
	Normal (n.)	0	0	0	6	9
Group III	Low (n.)	30	30	24	7	5
	Normal (n.)	0	0	6	23	24
P value		---	---	0.002*	<0.001*	<0.001*

Table 3. Cardiac output changes in all groups

		Baseline	Day 1	Day 3	Day 5	Day 7
Group I	Low (n.)	30	30	30	22	18
	Normal (n.)	0	0	0	5	5
Group II	Low (n.)	30	30	30	21	16
	Normal (n.)	0	0	0	6	9
Group III	Low (n.)	30	30	27	7	5
	Normal (n.)	0	0	3	23	24
P value		---	---	0.045*	<0.001*	<0.001*

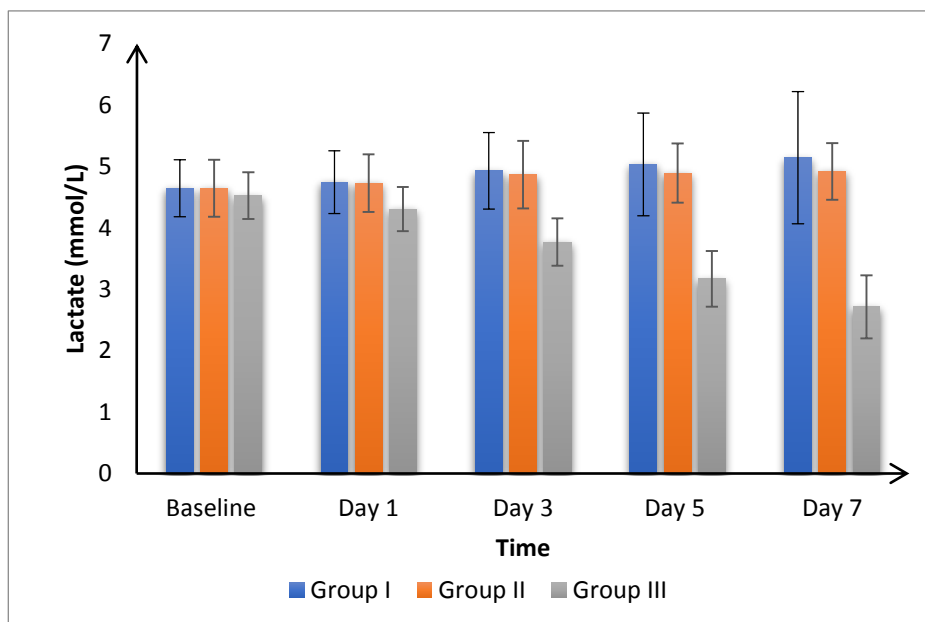


Fig. 4. Serum lactate level changes in all groups

Table 4. Comparison between length of ICU stay (days) in all groups

	Group I	Group II	Group III
Mean	16.6	11.3	9
± SD	8.37	2.26	0.83
P value	<0.001*		
P1	<0.001*		
P2	<0.001*		
P3	0.08		

28-day mortality was 15 patients in group I, 7 patients in group II and 2 patients in group III. Mortality was significantly lower in group II (P1 < 0.05) & group III (P2 < 0.001) compared to group I. While there was no statistically significant difference as regard 28-day mortality between group II & group III (P3 >0.05). Table 5.

4. DISCUSSION

Tachycardia promotes cardiac dysfunction by increasing oxygen requirements and diminishing diastolic cardiac filling and coronary perfusion. An estimated 50% of septic shock patients develop cardiomyopathy, as assessed by echocardiography [12]. Administration of bisoprolol could protect patients from toxicity of endogenous and exogenous catecholamines and improve cardiac function and homeostasis of immunologic and coagulation processes, however, some concerns about danger of reducing COP and blood pressure remained [13].

Controlling sinus tachycardia with ivabradine during septic shock would allow reducing cardiac metabolic demand and improving chronotropic tolerance of exogenous catecholamines without negative inotropic effects nor hypotension [14].

Results of the present study showed that both bisoprolol (5 mg once daily) & ivabradine (5 mg twice daily) effectively lowered HR in septic shock patients. Ivabradine was more effective than bisoprolol.

In agreement with our results, Qiu et al. [15] have studied the HR controlling effect of ivabradine versus some of β-blockers as a pretreatment before Computed Tomography Coronary Angiography. They have found better control of HR with ivabradine more than β-blockers.

Also Ghadimi et al. [16] in their study of comparing efficacy of ivabradine versus β-blockers in patients with mitral stenosis in sinus rhythm. Results showed remarkable reduction in HR at maximal exercise and HR at rest with ivabradine in comparison with β-blockers [16]. This was explained as ivabradine is a pure HR-

lowering agent that acts via selective and specific inhibition of the cardiac pacemaker I_f current, which controls spontaneous diastolic depolarization in sinus node and regulates HR. The cardiac effects are specific to the sinus node, with no effect on intra-atrial, atrioventricular, or intraventricular conduction times, myocardial contractility, or ventricular repolarization [16].

In contrast to our results, Nuding et al. [7] in their study comparing two groups of patients with multiple organ dysfunction syndrome (MODS) to receive standard treatment ± ivabradine (5 mg twice daily) for 4 days via enteral route. The primary outcome was percentage of patients with HR reduction after 4 days. Secondary outcomes included effect of ivabradine on hemodynamics, disease severity, vasopressor use, mortality, and adverse events. The results showed that there were no significant differences in HR reduction between ivabradine and control groups and also no difference in secondary outcomes were observed.

This might be due to the difference in the duration of treatment with ivabradine between the present study and the above study. Although early treatment, within the first 4 days, has the greatest potential to influence prognosis in these critically ill patients and elicit changes in surrogate parameters of mortality, it remains unclear whether treating patients longer than 4 days would influence HR changes [7].

Results of the present study showed that bisoprolol (5 mg once daily) and ivabradine (5 mg twice daily) did not affect MAP significantly, with ivabradine being more effective in maintaining blood pressure than bisoprolol. This is in agreement with Ibrahim and Atallah [17]. They gave ivabradine 5 mg at the night of operation & 1 hour before induction of anesthesia in comparison with propranolol 10 mg and then measured blood pressure before & after intubation & extubation. The results showed mild elevation in blood pressure and HR elevation in β-blocker group.

Table 5. Comparison between 28 day mortality in all groups

	Group I	Group II	Group III
Dead	15 (50%)	7 (23.3%)	2 (6.7%)
Alive	15 (50%)	23 (76.7%)	28 (93.3%)
P value	<0.001*		
P1	0.032*		
P2	<0.001*		
P3	0.146		

Also, Rimoldi et al. [18] who studied the effect of ivabradine on central blood pressure in stable coronary artery disease. They randomized patients into two groups (ivabradine & placebo). In placebo group, central systolic pressure and SV remained unchanged while patients on ivabradine showed an increase in central systolic pressure and in SV. This was explained as there was an inverse correlation between the decrease in HR and the increase in central systolic pressure, indicating that the greater the negative chronotropic effect of ivabradine, the greater was the increase in central pressure. Moreover, the HR-lowering effect of ivabradine was associated with an increase in SV without significant changes in COP. Conceivably, the observed increase in central pressure could be because of a ventricular–vascular mismatch or of an increase in SV. The observed increase in central pressure could also be related to an increased SV pumped into aorta [18].

Also, Morelli et al. [19] in their study of effect of HR control with esmolol on hemodynamics and clinical outcomes in patients with septic shock where they randomly assigned 77 patients to receive continuous infusion of esmolol titrated to maintain HR between 80/min and 94/min for their ICU stay and 77 patients to standard treatment. They found that MAP was maintained despite marked reduction in norepinephrine requirements in β -blocker group in comparison with control group. This was explained as lowering of HR by esmolol allows better ventricular filling during diastole, hence, improving SV and thereby improving the efficiency of myocardial work and oxygen consumption and consequently improving MAP [19].

On the other hand, Nuding et al. [7] in their study showed that there were no significant differences in MAP between ivabradine and control groups [7] This might be due to the difference in the duration of treatment with ivabradine between the present study and the above study.

Results of the present study showed that there was no statistically significant difference in NA dose between bisoprolol group & control group, while NA dose was significantly lower in ivabradine group in comparison with other two groups. This is in agreement with Liu et al. [20] who investigated 100 cases of septic shock patients with tachycardia. Patients in esmolol group received standard treatment plus esmolol injection with an initial dose of 25 mg/h. HR target was 80 to 100 b/m. Patients in esmolol group continued to use esmolol for 7 days or to the day patient left ICU when HR didn't achieve the target. Patients in control group were given standard treatment. Results showed that there was no significant difference in total doses of norepinephrine between both groups.

Also, De Santis et al. [21] who studied ivabradine use in three patients developed sepsis related MODS after cardiac surgery. They found that hemodynamic improvement resulted in reduction in noradrenaline dose. This was explained by ability of ivabradine to reduce HR with concomitant increase in stroke volume index, end diastolic volume index and central venous O₂ saturation. The hemodynamic improvement resulted in a consistent serum lactate level reduction and norepinephrine dosage.

On the other hand, Nuding et al. [7] showed that there were no significant differences in noradrenaline doses between ivabradine and control groups. This might be due to the difference in the duration of treatment with ivabradine between the present study and the above study.

As regard to SV & COP, results of the present study showed that there was significant improvement in ivabradine group in comparison with bisoprolol and control groups. This is in agreement with Rimoldi et al. [18] who studied the increase in central pressure could be because of ventricular–vascular mismatch or of an increase in SV. The observed increase in

central pressure could also be related to an increased SV pumped into aorta [18].

Also, Nguyen et al. [22] in their study on patients with low cardiac output syndrome treated by dobutamine after elective coronary artery bypass surgery where patients received either intravenous ivabradine or placebo. Treatment lasted until dobutamine weaning. Primary endpoint was proportion of patients achieving HR from 80 to 90 b/m. Secondary endpoints were invasive and non-invasive disturbed hemodynamic parameters and arrhythmia events. They found that SV & COP significantly increased in ivabradine group in comparison with placebo. This was explained as the decrease in HR caused by ivabradine was associated with concomitant increase in SV and COP due to prolonged diastolic time which improves left ventricular diastolic filling. The resulting improvement in SV was sufficient to compensate for the deleterious effect of tachycardia, caused by dobutamine use, on myocardial oxygen consumption as in patients with low COP state. It has been argued that most of the improvement in COP after dobutamine was due to the increase in HR. However, the benefit of improving oxygen delivery may be counterbalanced by the deleterious effect of tachycardia on myocardial oxygen consumption [22].

On the other hand, Nuding et al. [7] showed that there were no significant differences in SV or COP between ivabradine and control groups. This might be due to the difference in the duration of treatment with ivabradine between the present study and the above study.

Also, Morelli et al. [19] found that SV significantly increased in esmolol group in comparison with control group. This might be explained as esmolol has the advantage of being ultrashort-acting with a half-life of approximately 2 minutes. This simplifies titration against a predefined HR target and enables rapid resolution of any potential adverse effect after drug discontinuation [19].

As regard to serum lactate level, results of the present study showed that there was significant improvement in ivabradine group in comparison with bisoprolol and control groups. This is in agreement with Wu et al. [23] in their study in which patients who experienced new onset acute systolic HF as well as sinus tachycardia received ivabradine therapy (2.5 – 5 mg twice daily). Primary outcome was improvement of EF, secondary endpoints included HR changes at 48

h after first ivabradine administration vs. baseline, changes in B-type natriuretic peptide levels, blood pressure, liver and renal function, and plasma lactic acid changes prior to and after ivabradine use. Results showed improvement in serum lactate level after ivabradine therapy. This might be explained by the increase in SV due to prolonged time for diastolic filling; this increase leads to elevation in perfusion pressure to tissues, lowering anerobic metabolism and consequently serum lactate level [23].

Also, Morelli et al. [24] found in their study which investigated microcirculatory & macrocirculatory effects of reducing HR in septic shock using esmolol, where 25 septic shock patients with HR greater than 95 b/m requiring norepinephrine to maintain MAP greater than or equal to 65 mmHg received titrated esmolol infusion to maintain HR less than 95 b/m. Sublingual microcirculatory blood flow was assessed. Measurements included norepinephrine requirements and lactate level. MAP and lactate levels remain unchanged and authors claimed that small sample size might be a limitation.

On the other hand, Nuding et al. [7] in their study showed that there were no significant differences in serum lactate level between ivabradine and control groups. This might be due to the difference in the duration of treatment with ivabradine between the present study and the above study.

Also, Schmittinger et al. [25] in their study on 40 patients with septic myocardial depression. In all study patients, β -blockers were initiated only after stabilization of cardiovascular function in order to decrease HR to less than 95 b/m. Hemodynamic data and laboratory parameters were documented before and 6, 12, 24, 48, 72, and 96 hours after first β -blocker dosage. Adverse cardiovascular events were documented. Results showed that serum lactate significantly decreased as one of the surrogate markers of perfusion. This might be explained by the combination used in this study as they used milrinone which is a phosphodiesterase III inhibitor that was applied as an inotropic agent for all patients. Positive inotropic effects of milrinone are mediated through inhibition of the breakdown of cAMP by phosphodiesterases and act independently of β_1 receptors. The combination of milrinone and metoprolol may hold potential benefits for myocardial function and thus perfusion pressure and serum lactate as a surrogate [25].

As regard to LOS, results of the present study showed that controlling tachycardia in sepsis with both bisoprolol & ivabradine resulted in significant decrease in LOS.

This is in agreement with Nuding et al. [7] who found that there was significant decrease in ICU stay in ivabradine group Vs control [7]. Also, Morelli et al. [19] who studied effects of HR control by esmolol in patients with septic shock; there was significant decrease in LOS in esmolol group [19].

In contrast to our results, Schmittinger et al. [25] in their study on 40 patients with septic myocardial depression. Results showed that there was no significant difference in LOS between two groups.

As regard to 28-day mortality, results of the present study showed that controlling tachycardia in sepsis with both bisoprolol & ivabradine resulted in significant decrease in mortality. This is in agreement with Morelli et al. [19] who found that there was significant decrease in 28-day mortality in esmolol group [19].

In contrast to our results, Aileen et al. [26] who studied effect of ivabradine on major adverse cardiovascular events and mortality in critically ill patients. They searched Medline, Embase, Cochrane Library, and Web of Science for RCTs. Trial quality was assessed using the Cochrane risk of bias tool. They found that effect of ivabradine on mortality in acute care remains unclear and recommended further trials to detect changes in outcomes [26]. Also, Liu et al. [20] stated that there was no significant difference in 28 day mortality in both groups.

Limitations of the study were lack of IV formula of ivabradine and relatively small sample size.

5. CONCLUSIONS

Controlling HR in septic shock patients with either bisoprolol or ivabradine improves outcomes. Ivabradine is better than bisoprolol in maintaining hemodynamics and improving tissue perfusion parameters.

CONSENT AND ETHICAL APPROVAL

After approval of our institutional ethical committee, an informed written consent was obtained from the surrogates of all patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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