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Evaluation of the safety and efficacy of beta blockers in septic patients: a randomized control trial

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Abstract

Background: Sepsis is a common fatal complication of an infection. As part of the host response, sympathetic stimulation can result in many serious complications such as septic myocardial depression and metabolic, hematological, and immunological dysfunction. Treatment with beta blockers may reduce this pathophysiological response to infection, but the clinical outcomes are not clear.

Results: Our study showed a significant difference as regards decrease in heart rate in group B with P value < 0.001 compared to group A, besides a reduction in 28-day mortality (P value 0.0385) and ICU stay (P value < 0.001) in group B compared to group A.

Conclusion: This study supports the role of intravenous beta blockers in sepsis patients by decreasing heart rate without affecting the hemodynamics, in addition to decreasing 28-day mortality and ICU stay.

Keywords: Sepsis, Beta Blocker, Mortality, ICU

Background

Sepsis is the leading cause to life-threatening organ failure due to non-organized host response to infection (Seymour et al. 2016). Septic shock is a severe sepsis with cardiovascular and metabolic/cellular affection, which has an increased mortality rate. Septic shock can be diagnosed by a clinical evidence of sepsis with persisting hypotension that needs vasopressors to keep mean arterial blood pressure (MAP) more than or equal to 65 mmHg in addition to a serum lactate level more than 2 mmol/L not responding to proper volume resuscitation. This raises the hospital mortality to be more than 40% (Shankar-Hari et al. 2016).

During infection, the attacking pathogens interact with the patient's immune system initiating a downstream inflammatory sequence including the release

of cytokines and other mediators that in turn produce a generalized systemic response which includes activation of sympathetic nervous system activation and release of catecholamines stimulating beta adrenergic receptors in the heart increasing contractility, heart rate, and cardiac output in order to cope with the high metabolic demands needed to fight the infection (Favero et al. 2013).

However, this pathophysiological process can cause multi-organ failure, and further clinical deterioration occurs due to a global imbalance between systemic oxygen supply and demand. This imbalance is due to the excessive release of catecholamine that causes sepsis-induced myocardial dysfunction, decreasing left ventricular ejection fraction followed by vasodilation, altered vascular permeability, myocardial depression, and failure of the coagulation cascade (Kenney and Ganta 2014).

Beta blockers are mainly used to treat arrhythmias and to protect the ischemic heart from a second heart

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attack (myocardial infarction). Despite their wide use to treat hypertension, they are not the first choice for initial treatment of most patients any more (James et al. 2014).

Beta blockers could reduce the continuous sympathetic stimulation in septic shock and relieve its effects, improving the outcomes. They could alter the production of cytokines, improving the metabolic dysregulation by reducing protein catabolism and basal metabolic energy needs and inhibiting gluconeogenesis.

On the contrary, using beta blockers in sepsis has the possibility to be hazardous. Many patients with septic shock are treated by beta agonists as vasopressor and inotrope infusions so they could exacerbate hypotension and bradycardia exacerbating shock in these patients (Sanfilippo et al. 2015).

Aim of the study

Evaluate the efficacy and safety of the use of beta blockers in ICU patients with sepsis.

Methods

After approval of the research ethical committee and obtaining informed written consent from patients or their relatives, this prospective randomized controlled study was conducted. We enrolled 60 patients of age 18–60 years of both sexes and randomly divided them into 2 groups, 30 patients each. We enrolled patients diagnosed with septicemia with the following clinical evidence of infection upon ICU admission: the presence of polymorph nuclear cells in a normally sterile body fluid, culture or gram stain of blood, sputum, urine, or normally sterile body fluid positive for a pathogenic microorganism, focus of infection identified by visual inspection; patients with evidence of a systemic response to infection as defined by the presence of three or more of the following signs within the previous 24 h: fever $> 38.0^{\circ}\text{C}$ or hypothermia $< 36.0^{\circ}\text{C}$, tachycardia, and tachypnea or the patient requires mechanical ventilation—leukocytosis or leukopenia; and patients with disease leading to sepsis with or without evidence of either organ dysfunction or septic shock. Our exclusion criteria included patients who are not septic, refused participation, are with contraindication to use beta blockers, are with multi-organ failure on admission, and are on inotropes such as adrenaline and dobutamine.

Study procedures

During the assessment, all enrolled patients or relatives were informed about the study objectives and protocol. On admission and on daily basis, the following data were recorded: mean arterial blood pressure (every 4 h), heart rate (every 4 h), central

venous pressure (every 4 h), urinary output, and daily full laboratory investigations including complete blood count, kidney functions, liver functions, arterial blood gases (ABG) and chest X-ray, electrocardiogram (ECG), and echocardiography (on admission and when needed).

Patients were randomized by closed envelope method into 2 equal groups, each consisting of 30 patients namely group A (control) and group B (esmolol). In group A, patients received the standard of care for sepsis according to our hospital protocol (broad-spectrum antibiotics according to suspected focus, fluids to elevate CVP above 10 mmHg, vasopressors to keep MAP > 65 mmHg, pan-cultures). In group B, patients received the standard of care for sepsis in addition to esmolol intravenous infusion by starting dose of 0.05–0.2 mg/kg/min and the dose was titrated every 20 min. Decreasing heart rate below 55 with hypotension MAP < 65 despite the measure to maintain them requires stopping of the esmolol infusion till reversal of the condition then restarted again.

The primary outcome was the heart rate. Secondary outcomes were MAP, central venous oxygen saturation measured from the central venous line, central venous pressure, serum lactate, APACHE II score (on admission), SOFA recorded daily for the first week beside ICU stays (in days), and 28-day mortality.

Sample size

Using the PASS program, the alpha error was set at 5% and power at 80%. Results from the previous study (Du et al. 2016) showed that the heart rate before and after the use of IV esmolol was 107.8 ± 8.7 and 86.2 ± 10.2 , respectively, with P value 0.001. Based on this, the needed sample is 30 cases per group (60 total). The effect size was 2.27.

Statistical analysis

Data was analyzed. Statistical analysis was performed using computer software Statistical Package for the Social Science (SPSS, version 20; SPSS Inc., Chicago, IL, USA). Data were expressed as mean values \pm SD, numbers (%). Student's t test was used to analyze the parametric data, and discrete (categorical) variables were analyzed using the χ^2 test. Significance level (S) was set at a P value of 0.05 or less, and a P value of 0.01 or less was considered highly significant (HS).

Results

We enrolled 60 septic patients and randomly divided them into 2 groups: 30 patients in group A received the standard care of sepsis in addition to esmolol intravenous infusion by starting dose of 0.05–0.2 mg/

kg/min and the dose was titrated every 20 min, and in group B, patients received the standard care of sepsis.

There was no significant difference between the two groups regarding age, sex (Table 1), and admission hemodynamic and inflammatory variables (Table 2), mean arterial pressure (Table 3 and Fig. 1), central venous pressure (Table 4 and Fig. 2), central venous oxygen saturation measured from the central venous line sample (Table 5 and Fig. 3), serum lactate (Table 6 and Fig. 4), and APACHE II score (Table 2) and SOFA score (Table 7 and Fig. 5) during the first week.

Heart rate showed a significant reduction in group B compared to group A in days 1–6 (P value < 0.001) (Table 8 and Fig. 6).

There was a significant reduction in ICU stay (Table 9 and Fig. 7) and 28-day mortality (Table 9 and Fig. 8) of group B compared to group A (P value 0.001 and 0.0385, respectively).

Discussion

This randomized controlled study was conducted on 60 ICU patients with sepsis divided into 2 groups to compare the effect of IV beta blockers on hemodynamics and ICU stay and mortality. The results showed a significant difference regarding heart rate reduction being evident in the IV beta blocker group, also reduction of mortality and ICU stay being the lowest in patients who received IV beta blockers.

Although the mortality from septic shock has fallen in recent years, this has been through improved detection and earlier antibiotic therapy. In our study, we hypothesized the benefits of BB in patients with sepsis such as significant lowering in HR, ICU stay, and 28-day mortality.

There is a question of whether beta blockers could offer a way of treating the critically ill patient with septic shock? And if so, how its benefits may arise? Could it be due to that adrenergic system is a powerful stimulator of the immune system? (Elenkov et al. 2000).

Table 1 Comparison between both groups according to the demographic data

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test/ χ^2 *	P value
Age	56.4 ± 4.8	58.3 ± 5.7	1.397	0.167
Sex (male%)	23/30 (76.6%)	17/30 (56.6%)	-2.672*	0.102

*The result is done by chi square test because it is proportions comparison There was no statistically significant difference between both groups according to the demographic data as shown in Table 1

Table 2 Comparison between both groups according to admission data

Inflammatory variables	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test/ χ^2 *	P value
MAP mmHg	70.2 ± 6.42	72.3 ± 6.7	1.240	0.2201
HR rate/min	115.75 ± 12.86	113.4 ± 12.78	-0.710	0.4806
CVP CmH2o	11.7 ± 4.1	11.6 ± 2.6	-0.113	0.9106
ScvO2 %	76.2 ± 5.92	74.3 ± 4.8	-1.365	0.1774
Lactate	5.3 ± 1.35	5.2 ± 1.6	-0.262	0.7945
APACHE II	23.5 ± 6.2	24.2 ± 5.4	0.466	0.6427
SOFA score	9.2 ± 3.2	8.8 ± 3.5	-0.462	0.6458

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was no statistically significant difference between both groups according to admission data as shown in Table 2

Although there has been a great deal of focus on the cardiovascular benefits of beta blockade in sepsis, the ubiquitous nature of the adrenergic system brings Cohen et al. (2004) to question whether there are other mechanisms through which beta blockers may exert their influence (Rudiger 2010).

A single-center phase II study from Italy showed results that agree with ours by Morelli et al. (2013) who randomly assigned 77 patients to be treated by esmolol continuous infusion titrated to keep the heart rate between 80/min and 94/min for the duration of ICU stay and 77 patients are subjected to standard treatment. The results reported that beta-adrenergic blockade in patients who continued to have high heart rates after standard fluid resuscitation caused improvements in cardiovascular performance including heart rate, left ventricle stroke volume, and systemic vascular resistance index; serum lactate; and a decrease in vasopressor dependence, with no adverse effects (Morelli et al. 2013).

Table 3 Comparison between groups regarding MAP

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test	P value
Day 0	70.2 ± 6.42	72.3 ± 6.7	1.240	0.2201
Day 1	72.2 ± 5.92	71.6 ± 5.8	-0.397	0.6932
Day 2	70.4 ± 4.58	72 ± 6.1	1.149	0.2553
Day 3	70.61 ± 4.82	72.2 ± 5.79	1.156	0.2524
Day 4	70.53 ± 4.6	72.33 ± 5.46	1.381	0.1726
Day 5	71.31 ± 5.12	73.42 ± 5.38	1.556	0.1251
Day 6	72.1 ± 5.3	73.92 ± 5.02	1.366	0.1774

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was no statistically significant difference between both groups according to admission data as shown in Table 3 and Fig. 1

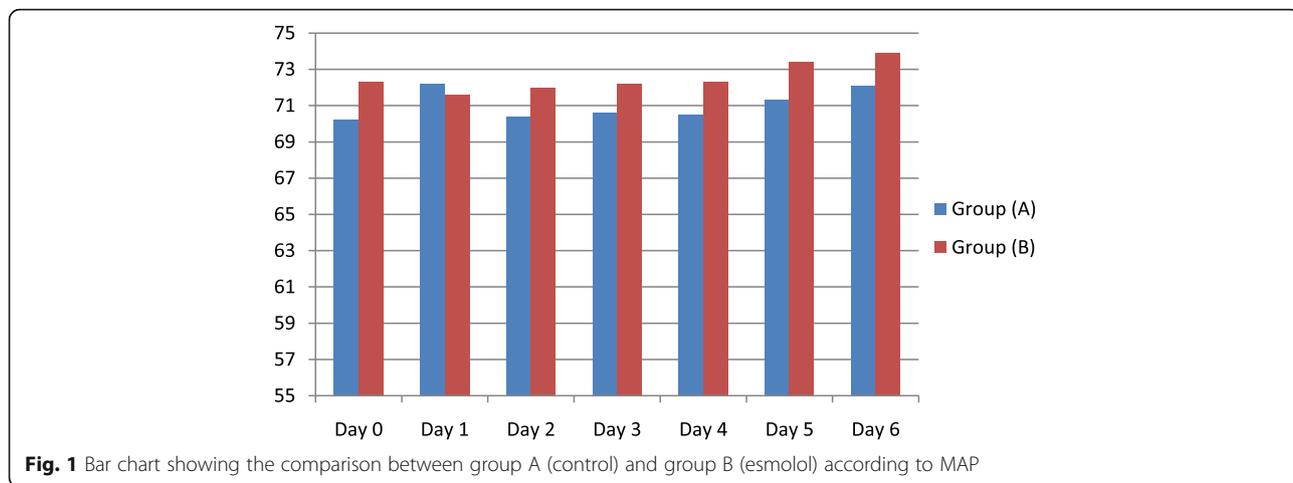


Table 4 Comparison between both groups regarding SOFA score

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test	P value
Day 0	9.2 ± 3.2	8.8 ± 3.5	-0.462	0.6458
Day 1	8.7 ± 3.9	8.4 ± 3.7	-0.306	0.7610
Day 2	8.5 ± 3.8	8.1 ± 4.2	-0.387	0.7003
Day 3	8.5 ± 3.6	8.3 ± 3.7	-0.212	0.8327
Day 4	7.9 ± 3.3	7.6 ± 3.9	-0.322	0.7489
Day 5	7.5 ± 2.9	7.3 ± 3.5	-0.241	0.8104
Day 6	7.6 ± 3.2	7.4 ± 3.1	-0.123	0.9026

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was no statistically significant difference between both groups according to the SOFA score as shown in Table 4 and Fig. 2

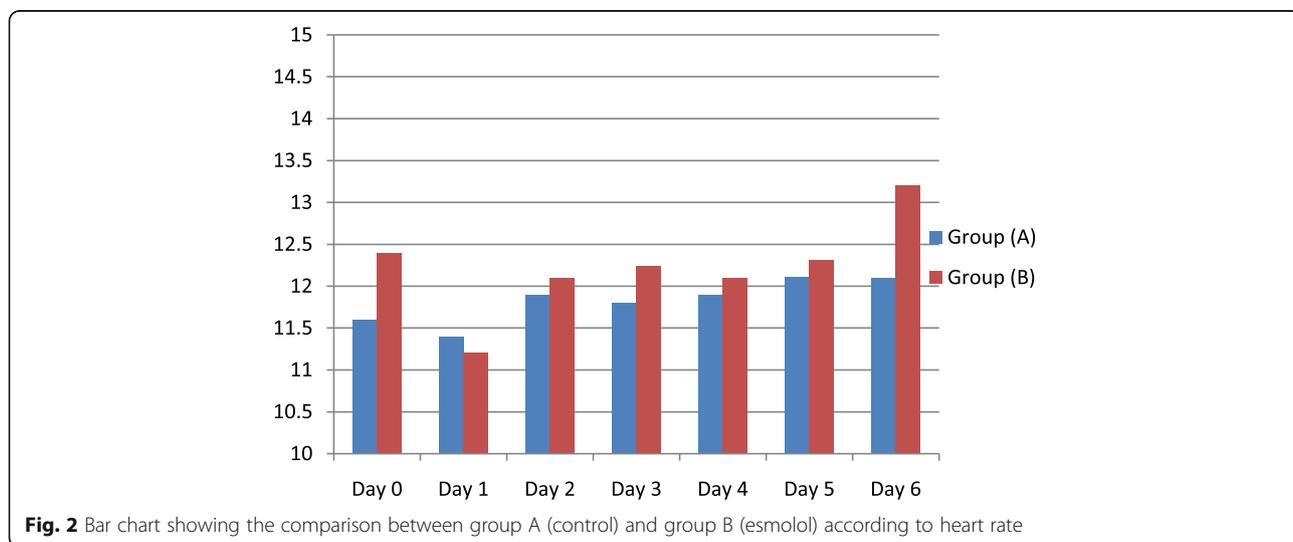


Table 5 Comparison between both groups according to heart rate

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test	P value
Day 0	115.75 ± 12.86	113.4 ± 12.78	- 0.710	0.4806
Day 1	114.63 ± 11.92	104.6 ± 9.65	- 3.582	< 0.001
Day 2	110.8 ± 10.2	94.2 ± 8.5	- 6.848	< 0.001
Day 3	108.5 ± 7.1	89.7 ± 5.9	- 11.154	< 0.001
Day 4	105.7 ± 6.9	88.2 ± 5.77	- 10.657	< 0.001
Day 5	103.2 ± 6.48	85.33 ± 5.56	- 11.463	< 0.001
Day 6	99.7 ± 6.11	82.21 ± 6.42	- 10.809	< 0.001

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

Heart rate showed a significant reduction in group B compared to group A in days 1-6 (P value < 0.001) as shown in Table 5 and Fig. 3

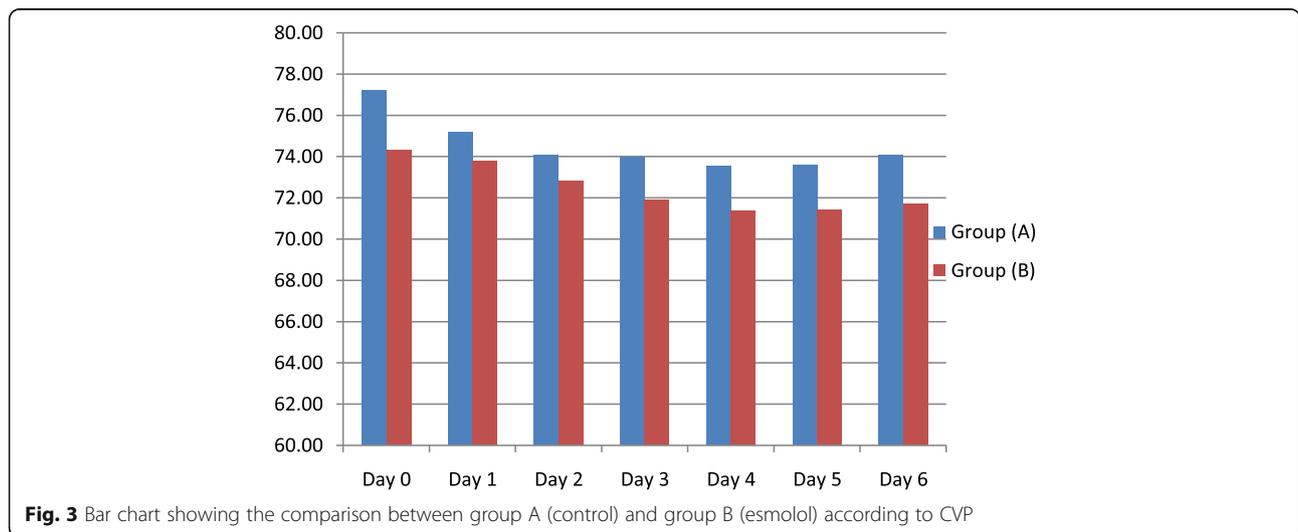


Fig. 3 Bar chart showing the comparison between group A (control) and group B (esmolol) according to CVP

Table 6 Comparison between both groups according to CVP

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test	P value
Day 0	11.7 ± 4.1	11.6 ± 2.6	- 0.113	0.9106
Day 1	10.9 ± 3.8	11.4 ± 2.3	0.617	0.5399
Day 2	11.4 ± 3.6	11.9 ± 2.6	0.617	0.5398
Day 3	11.7 ± 3.62	11.8 ± 2.41	0.126	0.9002
Day 4	11.9 ± 3.53	12.1 ± 2.3	0.260	0.7958
Day 5	12.11 ± 3.12	12.31 ± 2.32	0.282	0.7791
Day 6	12.1 ± 3.25	13.2 ± 2.71	1.424	0.1599

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was no statistically significant difference between both groups according to CVP as shown in Table 6 and Fig. 4

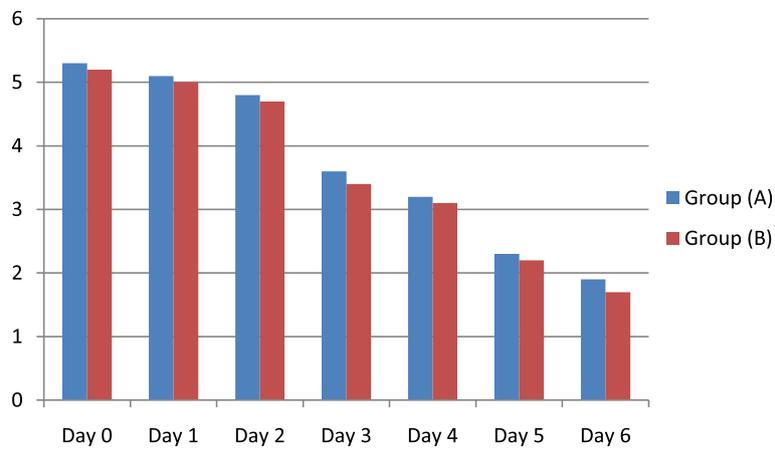


Fig. 4 Bar chart showing the comparison between group A (control) and group B (esmolol) according to ScvO2 %

Table 7 Comparison between both groups according to ScvO2 %

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test	P value
Day 0	77.2 ± 6.1	74.3 ± 4.8	- 1.365	0.1774
Day 1	75.2 ± 7.3	73.8 ± 5.6	- 0.833	0.4080
Day 2	74.1 ± 6.1	72.8 ± 4.7	- 0.925	0.3590
Day 3	74 ± 5.3	71.9 ± 4.2	- 1.701	0.0943
Day 4	73.52 ± 4.91	71.38 ± 3.57	- 1.931	0.0584
Day 5	73.6 ± 5.1	71.4 ± 3.6	- 1.930	0.0585
Day 6	74.1 ± 5.4	71.73 ± 4.2	- 1.898	0.0627

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was no statistically significant difference between both groups according to ScvO2 % as shown in Table 7 and Fig. 5

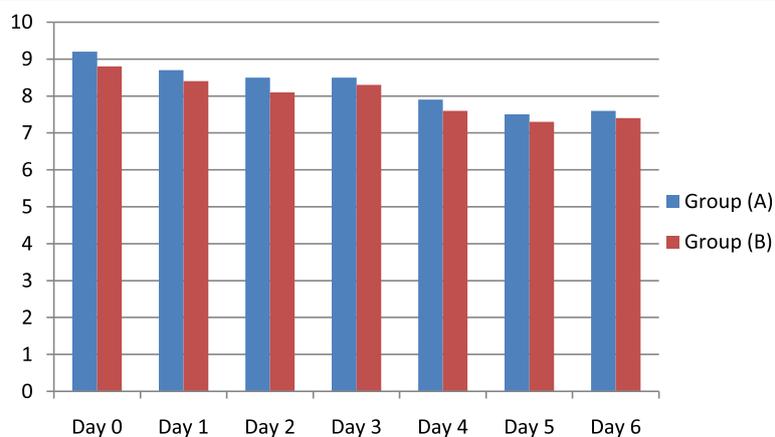


Fig. 5 Bar chart showing the comparison between group A (control) and group B (esmolol) according to lactate

Table 8 Comparison between both groups according to serum lactate

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test	P value
Day 0	5.3 ± 1.35	5.2 ± 1.6	- 0.262	0.7945
Day 1	5.1 ± 0.9	5.0 ± 1.1	- 0.385	0.7014
Day 2	4.8 ± 0.8	4.7 ± 1.2	- 0.380	0.7055
Day 3	3.6 ± 0.78	3.4 ± 0.59	- 1.120	0.2673
Day 4	3.2 ± 0.37	3.1 ± 0.4	- 1.005	0.3190
Day 5	2.3 ± 0.34	2.2 ± 0.26	- 1.280	0.2058
Day 6	1.9 ± 0.46	1.7 ± 0.35	- 1.895	0.0631

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was no statistically significant difference between both groups according to serum lactate as shown in Table 8 and Fig. 6

Agreeing with our results is a secondary analysis of a prospective observational single-center trial by Fuchs et al. (2017) who compared mortality rates between adult patients with severe sepsis or septic shock, in whom chronic beta blocker therapy was continued and discontinued, respectively. A total of 296 patients with severe sepsis or septic shock and on chronic oral beta blocker were included. Chronic beta blocker was stopped during the acute phase of sepsis in 129 patients and continued in 167 patients. Continuation of beta blocker was associated with a decreased hospital, 28-day, and 90-day mortality rates in contrast to their discontinuation (Fuchs et al. 2017).

Also in the side of our results, Fuchs et al. (2015) performed an observational, single-center cohort study of intensive care unit (ICU) patients with primary severe sepsis or septic shock. They included 580 adult patients. Cessation of a pre-existing treatment with beta blockers during sepsis therapy was attributed to increased 90-day mortality of 71% compared to 42% in patients with

ongoing therapy ($P < 0.001$). In contrast, newly started oral beta blockers decreased the 90-day mortality from 42% in patients without beta blocker therapy before and during sepsis to 28% ($P < 0.05$). They concluded that chronic beta blocker therapy should continue in patients with severe sepsis and septic shock. In addition, the newly started beta blocker therapy should be considered in septic patients after stabilization (Fuchs et al. 2015).

Balik et al. (2012) enrolled ten septic patients who were given esmolol drip. The heart rate decreased from mean 142 ± 11 /min to 112 ± 9 /min ($P < 0.001$) with parallel insignificant reduction of the cardiac index. Twenty-eight-day mortality was 10% (1/10) (Balik et al. 2012).

Du et al. (2016) recruited 63 septic shock patients from the intensive care unit of Peking Union Medical College Hospital. After starting esmolol therapy, blood pressure was not altered, whereas stroke volume (SV) improved compared with that before esmolol therapy ($P = 0.047$), and lactate levels

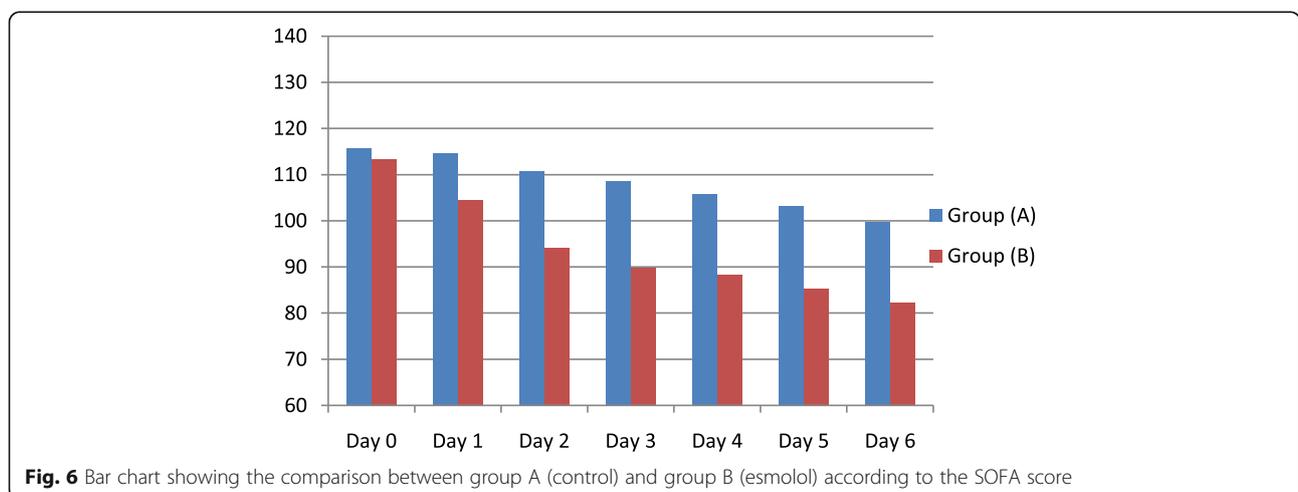


Fig. 6 Bar chart showing the comparison between group A (control) and group B (esmolol) according to the SOFA score

Table 9 Comparison between both groups according to ICU stay and 28-day mortality

	Group A: control (n = 30)	Group B: esmolol (n = 30)	t test/ χ^2	P value
ICU stay (days)	16.2 ± 3.2	13.2 ± 3.31	- 3.569	< 0.001
28-day mortality (no)	21/30	14/30	- 4.282	0.0385

Data presented as mean ± SD

P value > 0.05 NS; *P value < 0.05 S; **P value < 0.001 HS

There was a significant reduction in ICU stay and 28-day mortality of group B compared to group A (P value 0.001 and 0.0385, respectively) as shown in Table 9, Figs. 7 and 8

(P = 0.015) were also reduced after esmolol therapy (Du et al. 2016).

Agreeing with our results, Shang et al. (2016) conducted a randomized control study of 151 patients with severe sepsis who were enrolled and divided into the esmolol group (n = 75) and the control group (n = 76) that were treated by standard antiseptic shock measures. The esmolol group was treated by continuous IV infusion of esmolol. The results showed that esmolol reduced heart rates and the duration of mechanical ventilation in patients with severe sepsis, with no hazardous effect on circulatory function or perfusion (Shang et al. 2016).

Lee et al. (2019) and Li et al. (2020) both systematic review showed results agreeing with our results, decreasing both heart rate and mortality in patients receiving beta.

On the contrary, Al Harbi et al. (2018) conducted a nested cohort study in which all medical-surgical ICU patients (N = 523) were grouped according to beta-blocker use during ICU stay. The primary endpoints were all-cause ICU and hospital mortality. Their results showed that 89 (17.0%) were treated by beta-blockers during their ICU stay.

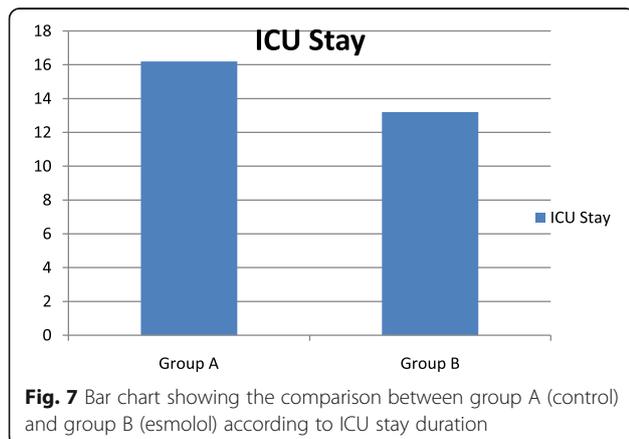


Fig. 7 Bar chart showing the comparison between group A (control) and group B (esmolol) according to ICU stay duration

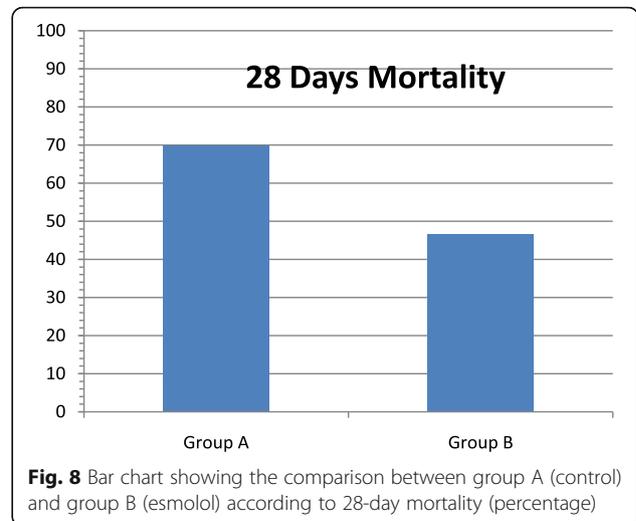


Fig. 8 Bar chart showing the comparison between group A (control) and group B (esmolol) according to 28-day mortality (percentage)

There was no significant attribution between beta-blocker therapy and ICU mortality (P = 0.16), hospital mortality (P = 0.73), or ICU length of stay (P = 0.22). However, beta-blocker use was related to the increase in ICU and hospital mortality among non-diabetic patients. This controversy could be associated due to the exclusion of type I diabetes, diabetic ketoacidosis, pregnancy, “do-not-resuscitate” status within 24 h of admission, terminal illness, admission to the ICU after cardiac arrest, seizures, liver transplantation, and/or burn injury (Al Harbi et al. 2018).

Conclusion

We concluded that beta blocker use in ICU septic patients decreased heart rate, ICU stay, and 28-day mortality.

Abbreviations

ABG: Arterial blood gases; APACHE II: Acute Physiology and Chronic Health Evaluation; CVP: Central venous pressure; HR: Heart rate; ICU: Intensive care unit; MAP: Mean arterial pressure; RBS : Random blood sugar; ScvO2 %: Saturation central venous oxygen; SOFA: Sequential Organ Failure Assessment Score; SV: Stroke volume

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Not applicable.

Authors’ contributions

RG and DI designed the study and revised the literature. HZ critically reviewed the manuscript. EA analyzed the data and wrote and critically revised the manuscript. MA followed up the patients, collected the data, performed the analysis, and wrote the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approval of the research ethical committee of Faculty of Medicine, Ain-Shams University, was obtained (code number: FMASU MD (69/2018), approval date 28 February 2018), and written informed consent was obtained from patients and/or their first-degree relatives.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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