ABENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

The Outcome of Using First Oral Funny Current Inhibitor Drug in Septic Shock Patients

Samir E. Ibrahim [a], Ehab A. Abdelrahman [a], Muhammad H. Hagr [a], Emad F. Rizk [b]

[a] Department of anesthesia and intensive care Faculty of Medicine Benha University, Egypt. [b] Department of Critical Care Medicine,, Faculty of Medicine Benha University, Egypt.

Corresponding to: Muhammad H. Hagr Department of Critical Care Medicine, Faculty of Medicine Benha University, Egypt.

Email: dr.medo2017@yahoo.com

Received:

Accepted:

Abstract

Background: Septic shock is a subtype of sepsis that is clinically identified by a requirement for the administration of vasopressors to increase the mean arterial blood pressure to 65 mmHg or greater despite sufficient fluid resuscitation, or by an increase in serum lactic acid levels by 2 mmol/L or greater. **This study aimed to** evaluate the effect of the cardiac pacemaker current inhibitor ivabradine on heart rate and outcome in patients with septic shock. **Methods:** A prospective, single blinded randomized controlled clinical trial study conducted on 102 septic shock patients. **Results:** regarding regression analysis indicated that Age, APACHE II, Sofa at (4th, 7th day), MAP at 4th day, NE at (4th, 7th day), HR at 4th day and ICU stay was the most factor affected mortality rate in patients with septic shock ($P<0.05$). Tachycardia The administration of enteral ivabradine to patients with septic shock and persistent tachycardia resulted in a significant reduction in heart rate and vasopressor requirements, and an improvement in cardiac and microcirculatory function parameters, without an increase in adverse events. **Conclusion:** It is suggested that ivabradine is an effective, safe, and cost-effective agent for heart rate control in septic shock and our results confirm the potential beneficial effects of Ivabradine administration during septic shock as it improves autonomic control of HR and modulation of HR oscillations but not affects 15 days survival or length of stay in ICU.

Key words: Funny current Inhibitor; Vasopressor; Septic Shock; Tachycardia

Introduction

Tachycardia is a key compensatory mechanism in septic shock. Many patients, however, develop refractory tachycardia, which persists despite correction of hypovolemia with fluids and vasopressors. This may be the result of excessive sympathetic stimulation from endogenous and exogenous sources, or due to the direct effect of bacterial endotoxins and inflammatory mediators on the sinoatrial node (SAN), [1 & 2] . Evidence suggests that persistent tachycardia may be harmful for patients with septic shock [3].

Ivabradine is the first cardiac pacemaker current (funny current) inhibitor that lowers heart rate without any negative effect on cardiac conductivity or contractility. Ivabradine has been evaluated for heart rate control in patients with acute decompensated heart failure and cardiogenic shock, with promising results [4 & 5].

Ivabradine is a cardiotonic agent used for the symptomatic management of angina pectoris. It is taken orally or crushed then infused through nasogastric tube twice daily. Ivabradine was approved by the European Medicines Agency in 2005 [6]. Some preliminary findings suggest that ivabradine may be useful in the management of patients with septic shock [7].

So, the aim of the study was to evaluate the effect of the cardiac pacemaker current inhibitor ivabradine on heart rate and outcome in patients with septic shock.

Patient and methods

A prospective, single blinded randomized controlled clinical trial study conducted on 102 septic shock patients who were non-randomly selected and this study was carried out in Intensive Care department Benha University. The period was 9 months from June 2022 to February 2023.

Ethics approval and consent to participate: A signed informed consent was obtained from the subject after a brief and detailed description of the study's goals. The consent form was created in compliance with the Helsinki Declaration and the Quality and Improvement System requirements set forth by the Egyptian Ministry of Health. The local ethical scientific committee of Benha Faculty of Medicine in Qalubyia, Egypt, gave its approval to the study plan.

Sample size: The sample size is calculated by Open Epi version 3.01. Confidence intervals 95%, power of the study 80% according to Effectiveness of enteral ivabradine for heart rate control in septic shock: a randomized controlled trial. The calculated minimal sample size is 102 patients, these patients was divided to two groups: **Case group:** septic shock patients was treated with ivabradine (dose of 5 mg /12 hrs) orally or crushed then infused through nasogastric tube beside regular management. **Control group:** septic shock patients were treated with regular management without using ivabradine.

Inclusion criteria:

Age from 18 to 75 years of age, proven or suspected site of infection clinically, laboratory and radiologically, septic shock (defined as hypotension not responding to fluid resuscitation and requiring norepinephrine of dose up to 0.4 Mic/kg/min to maintain adequate blood pressure) and in sinus rhythm with heart rate more than 100 bpm.

Exclusion criteria:

Age less than 18 years or more than 75 years of age, patients with pre-existing cardiovascular disease (coronary artery disease, congestive heart failure, cardiac rhythm abnormalities and conduction defects, congenital heart disease or pacemaker in situ, acute coronary

syndrome), sever renal failure (creatinine clearance<15ml/min), liver impairment (Child-Pugh class C), pregnancy or breast feeding, known allergy to ivabradine, co-treatment with bradycardic agents as beta blockers or drugs inducing qt prolongation, contraindication to enteral feeding or malabsorption syndrome, patients with hemoglobin less than 9 g/dl or active bleeding, patients with body mass index (BMI) more than 35 kg/m2, patients requiring the use of potent cytochrome p450 3a4 inhibitors such as antifungals of the azole-type, macrolide antibiotics and HIV protease inhibitors, patients requiring high dose noradrenaline (more than 0.4 mic/kg/min) or a second vasopressor to maintain map more than 65 mmhg, patients with known seizure disorder, electrolyte imbalance (serum k <3.5 mmol/l or >5.5 mmol/l ,serum NA <130 mmol/l or >150 mmol/l , serum mg <1.8 mmol/l) and mechanically ventilated patients.

Methods:

All patients were subjected to the following: Full history taking including: Age and sex

Medical history includes diabetes mellitus, hypertension, chronic kidney disease, ischemic heart disease and chronic liver disease.

Study tools & procedure: Study will be based on APACHE II score (is a general measure of disease severity based on current physiologic measurements, age & previous health conditions) after 24 hrs. From admission to determine critically ill patients 'organ function, the study will be carried on septic shock patients with heart rate more than 100 BPM and requiring norepinephrine infusion of dose up to 0.4 mic/kg/min to maintain mean arterial pressure (MAP) more than 65 mmHg in spite of adequate volume resuscitation afterobtaining pan cultures then starting broad spectrum antibiotics, taking full medical history & clinical examination on admission including heart rate, respiratory rate, blood pressure, temperature and conscious level according to Glasgow coma scale, routine laboratory profile which includes (CBC, liver profile, renal function tests, coagulation profile, serum lactate and electrolytes) on admission, day 4 and day 7, ECG and Echo on admission, detection of source of sepsis e.g. (pneumonia, urinary tract infection, infected wound, abdominal sepsis, brain abcess) and All patients will be followed up to 15 days after enrolment. The primary outcome is to detect heart rate and clinical improvement regarding SOFA score by following up both heart rate and SOFA score at day 1, 4 and 7 of admission. Secondary outcomes included the effect of ivabradine on length of ICU stay according to the equation of (Length of stay of one patient = date of discharge - date of) and 15-day overall survival.

Statistical Analysis:

Results were tabulated and statistically analyzed using a standard computer program using MICROSOFT EXCEL 2019 and SPSS V.25 program for MICROSOFT WINDOWS 10. **Two types of statistics were done: Descriptive statistics:** that includes the following test: The description of data was in the form of mean (±) SD for quantitivelydata, and frequency and

proportion for qualitative data and the mean is the sum of all observations by the number of observations.While standard deviation is a measure of the degree of scatter of individual varieties around their means.

Analytical statistics: Chi-Squared (χ^2), standard student-t test (t) and Mann-Whitney test (U).

Approval code: Ms23-7-2022

Results:

Our results showed that, there was no significant difference among the studied groups regarding age comorbidity and source of sepsis (P>0.05), there was no significant difference among the studied groups regarding APACHE II (P=0.674) and sequential organ failure assessment at 1st, 4th and 7th were significantly decreased among ivabradine group (11.96±2.34, 9.84±2.91, 7.69±4.61) than control group (13.00±1.47, 13.04±4.15, 12.84±6.90) respectively, (P<0.05) **[Table 1].**

Additionally, mean arterial pressure at 1st was significantly decreased among the ivabradine group (66.41±2.96) than control group (68.52±3.53), (P=0.001). While, there was no significant difference among the studied groups regarding mean arterial pressure at 4th and 7th (P>0.05), heart rate at 1st, 4th and 7th were significantly decreased among ivabradine group (126.43±3.81, 100.67±5.11, 83.48±5.33) than control group (127.75±2.30, 115.93±2.84, 108.57±4.51) respectively, (P<0.05) and NE at 1st, 4th and 7th were significantly decreased among ivabradine group (0.24±0.08, 0.08±0.13, 0.05±0.14) than control group (0.30±0.04, 0.16±0.15, 0.15±0.19) respectively, (P<0.05) **[Table 1].**

Moreover, ICU stays was significantly increased among ivabradine group (13.14±2.21) than control group (11.39±2.10), (P=0.006). Also, there was significant difference among the studied groups regarding outcome at 7 days (P=0.027), 82.4% of ivabradine patients still alive and 17.6% of patients dead. While there was no significant difference among the studied groups regarding 15 days survival (P=0.154) **[Table 1].**

In addition that, among ivabradine group, age was significantly increased among mortality (64.96±6.83) than improved (47.83±11.43), (P<0.001) and the most comorbidity was DM and HTN, DM found in (25.0%) of mortality and in (26.1%) of improved, HTN found in (25.0%) of mortality and in (4.3%) of improved with significant difference among the studied groups (P=0.005). While there was no significant relation among the mortality and improved groups regarding source of sepsis (P=0.071) **[Table 2].**

Moreover, among ivabradine group, APACHE II was significantly increased among mortality (27) than improved (22), (P=0.001), there was no significant relation among the mortality and improved groups regarding sequential organ failure assessment at (1st, 7th day), mean arterial pressure at (1st, 7th days), Ne at (1st, 4th and 7th day) and heart rate at (1st and 7th day), (P>0.05), sequential organ failure assessment at 4th day was significantly increased among mortality (10) than improved (9), (P=0.023), mean

arterial pressure at 4th day was significantly decreased among mortality (72.5) than improved (75), (P=0.004) and heart rate at 4th day was significantly increased among mortality (103.2) than improved (100), (P=0.024) **[Table 2].**

In addition, among the ivabradine group, ICU stays was significantly increased among the mortality group (13.14±2.21) than improved group (11.39±2.10), (P=0.006). Also, there was significant relation among the mortality and improved groups regarding outcome at 7 days (P=0.024) **[Table 2].**

Also, among control group, age was significantly increased among mortality (58.49±10.12) than improved (48.31±9.15), (P<0.05), the most comorbidity was DM and HTN, DM found in (28.6%) of mortality and in (18.8%) of improved, HTN found in (14.3%) of mortality and in (31.3%) of improved with significant relation among the mortality and improved groups (P=0.015). While there was no significant relation among the mortality and improved groups regarding source of sepsis (P=0.745) **[Table 3].**

Moreover, among control group, APACHE II was significantly increased among mortality (28) than improved (21), (P<0.001), There was no significant relation among the mortality and improved groups regarding sequential organ failure assessment at (1st day), mean arterial pressure at (1st, 4th, and 7th day) and heart rate at 1st day (P>0.05). While, sequential organ failure assessment 4th and 7th day were significantly increased among mortality (16, 20) than improved (10, 7.5) respectively, (P<0.001), Ne at 1st, 4th and 7th day were significantly increased among mortality (0.32, 0.33, 0.4) than improved (0.28, 0.05, 0.0) respectively, (P<0.05) and heart rate at 4th and 7th day were significantly increased among mortality (117, 110.7) than improved (115, 105) respectively, (P<0.05) **[Table 3].**

Also, among the ivabradine group, there was no significant relation among the mortality and improved groups regarding ICU stays (P=0.149). On the other hand, there was significant relation among the mortality and improved groups regarding outcome at 7 days (P<0.001) **[Table 3].**

Also, regarding regression analysis indicated that Age, APACHE II, Sofa at (4th, 7th day), MAP at 4th day, NE at (4th, 7th day), HR at 4th day and ICU stay was the most factor affected mortality rate in patients with septic shock (P<0.05) **[Table 4].**

Table (1): Demographic, clinical data and APACHE II score, sequential organ failure assessment hemodynamic data, and outcome among the studied groups (n=102).

Variable	Ivabradine Group (N=51)		Control Group (N=51)		*t*	*P value*	*MA*	Hemodynamic data		*U*	P value
							Variable	Ivabradine Group (N=51)	Control Group (N=51)	*t*	*P value*
Age/years	57.24±12.53		55.29±10.84		0.837	0.405	*MAP 1st day*	66.41±2.96	68.52±3.53	***3.273***	0.001*
Mean ±SD							*Mean± SD*	66.7 (58.3-73)	69 (61-75.3)		
Range	27-75		32-72				*Median (IQR)*				
Comorbidity	**N**	**z%**	**N**	**%**	$X^{2=}$	0.099	*MAP 4th day*	74.05±3.08	74.12±2.69	***0.125***	0.901
DM					13.408		*Mean± SD*	74.3 (67.3-82)	74 (69-79.7)		
HTN							*Median (IQR)*				
HTN,DM											
HTN,IHD											
CKD,HTN	13	25.5	13	25.5			*MAP 7th day*	74.93±3.15	75.19±2.88	***0.438***	0.662
DM,CKD	8	15.7	10	19.6			*Mean± SD*	74.7 (68-82)	74.7 (70-81)		
DM,IHD	7	13.7	10	19.6			*Median (IQR)*				
DM,HTN,CKD	2	3.9	4	7.8							
IHD	5	9.8	0	0.0			*Paired t test*	P1<0.001* P2<0.001* P3= 0.087	P1<0.001* P2<0.001* P3= 0.046*		
	0	0.0	2	3.9							
	4	7.8	0	0.0							
	1	2.0	0	0.0							
	1	2.0	1	2.0							
							HR 1st day	126.43±3.81	127.75±2.30	***2.111***	0.037*
							Mean± SD	126.3 (119.7-136)	127.7 (121.7-132.7)		
							Median (IQR)				
Source of sepsis	10	19.6	4	7.8	$X^{2=}$	0.177	*HR 4th day*	100.67±5.11	115.93±2.84	***18.631***	<0.001*
UTI	23	45.1	20	39.2	8.938		*Mean± SD*	102 (86.3-108)	116 (110.3-126)		
Pneumonia	5	9.8	6	11.8			*Median (IQR)*				
Soft tissue	5	9.8	10	19.6							
Abdominal sepsis	3	5.9	7	13.7							
Catheter related	1	2.0	3	5.9			*HR 7th day*	83.48±5.33	108.57±4.51	***25.659***	<0.001*
Obstetrics	4	7.8	1	2.0			*Mean± SD*	28.4 (72.7-93.3)	108.7 (100.7-118.7)		
CNS infection							*Median (IQR)*				
APACHE II	25.06±5.29		24.65±4.52		0.422	0.674	*Paired t test*	P1<0.001* P2<0.001* P3<0.001*	P1<0.001* P2<0.001* P3<0.001*		
Mean± SD											
Median (IQR)	24 (15-36)		24 (16-32)								
Sofa 1st day	11.96±2.34		13.00±1.47		2.685	**0.008***	*NE 1st day*	0.24±0.08	0.30±0.04	***5.276***	<0.001*
Mean± SD			14 (10-16)				*Mean± SD*	0.2(0.1-0.4)	0.3 (0.2-0.4)		
Median (IQR)	12 (7-18)						*Median (IQR)*				
Sofa 4th day	9.84±2.91		13.04±4.15		4.503	**<0.001***	*NE 4th day*	0.08±0.13	0.16±0.15	***2.934***	0.004*
Mean± SD	9 (6-20)		12 (8-20)				*Mean± SD*	0.03 (0.0-0.4)	0.06 (0.02-0.4)		
Median (IQR)							*Median (IQR)*				
Sofa 7th day	7.69±4.61		12.84±6.90		4.436	**<0.001***	*NE 7th day*	0.05±0.14	0.15±0.19	***2.736***	0.007*
Mean± SD	6 (3-22)		9 (4-22)				*Mean± SD*	0.0 (0.0-0.4)	0.0 (0.0-0.4)		
Median (IQR)							*Median (IQR)*				
Paired t test	P1<0.001* P2<0.001* P3<0.001*		P1=0.945 P2=0.866 P3=0.672				*Paired t test*	P1<0.001* P2<0.001* P3<0.001*	P1<0.001* P2<0.001* P3=0.004*		

Variable	Outcome				t	*P* value
ICU stays/days Mean ±SD Range	13.14±2.21 8-16		11.39±2.10 8-16		2.893	**0.006***
Outcome at 7 days	**N**	**%**	**N**	**%**	$X^{2=}$	**0.027***
Still	42	82.4	32	62.7	4.923	
Mortality	9	17.6	19	37.3		
15 days survival	28	54.9	35	68.6	$X^{2=}$	0.154
Mortality	23	45.1	16	31.4	2.034	
Improved						

DM: Diabetes mellitus, **HTN:** hypertension, **CKD:** chronic kidney disease, **IHD**: ischemic heart disease, X^2**:** Chi square, **UTI:** urinary tract infection, **t**: independent test, **CNS**: central nervous system, **SOFA:** Sequential organ failure assessment**, APACHE II:** Acute physiology and chronic health Evaluation II, **HR:** heart rate**, MAP:** Mean arterial pressure**, ICU:** intensive care unit, X^2**:** chi square, **t:** independent test. U: Mann–Whitney U test, *: significant

P1: 1^{st} Vs 4^{th}
P2: 1^{st} Vs 7^{th}
P3: 4^{th} Vs 7^{th}

Table (2): Demographic, clinical data, diagnosis, and outcome in relation to 15 days survival among the ivabradine group (n=51).

Variable	Ivabradine Group				t	*P* value
	Mortality (N=28)		**Improved (N=23)**			
Age (Mean ±SD)	64.96±6.83		47.83±11.43		6.321	**<0.001***
Comorbidity	**N**	**%**	**N**	**%**	$X^{2=}$	**0.005***
DM	7	25.0	6	26.1	5.493	
HTN	7	25.0	1	4.3		
HTN,DM	5	17.9	2	8.7		
HTN,IHD	1	3.6	1	4.3		
CKD,HTN	2	7.1	3	13.0		
DM,IHD	3	10.7	1	4.3		
DM,HTN,CKD	1	3.6	0	0.0		
IHD	1	3.6	0	0.0		
Source of sepsis	3	10.7	7	30.4	$X^{2=}$5.58	0.071
UTI	14	50.0	9	39.1	4	
Pneumonia	4	14.3	1	4.3		
Soft tissue	3	10.7	2	8.7		
Abdominal sepsis	2	7.1	1	4.3		
Catheter related	0	0.0	1	4.3		
Obstetrics	2	7.1	2	8.7		
CNS infection						
Variable	**Diagnosis in relation to 15 days survival**				***U***	***P value***
	Mortality (N=28) Median (IQR)		**Improved (N=23) Median (IQR)**			
APACHE II	27 (18-36)		22 (15-32)		3.669	**0.001***
Sofa 1st day	11.5 (10-18)		12 (7-16)		0.601	0.551
Sofa 4th day	10 (6-20)		9 (6-16)		2.352	**0.023***
Sofa 7th day	6 (3-22)		6 (4-18)		1.427	0.161
MAP 1st day	66.4 (61.7-73.0)		67.3 (58.3-72.3)		0.220	0.826
MAP 4th day	72.5 (67.3-78.7)		75 (71-82)		2.994	**0.004***
MAP 7th day	74.5 (68-82)		75 (69.7-81.0)		1.087	0.283
NE 1st day	0.2 (0.11-0.40)		0.2 (0.13-0.40)		0.292	0.772
NE 4th day	0.04 (0.00-0.40)		0.03 (0.00-0.40)		2.004	0.052
NE 7th day	0.0 (0.00-0.40)		0.0 (0.00-0.40)		1.895	0.065
HR 1st day	126.5 (120.3-135.3)		126 (119.7-136.0)		0.563	0.576
HR 4th day	103.2 (92.7-108.0)		100 (86.3-106.7)		2.344	**0.024***
HR 7th day	83.3 (72.7-93.3)		85 (75.0-93.3)		0.085	0.932

Variable	Outcome				*t*	*P* value
	Mortality (N=28)		Improved (N=23)			
ICU stays Mean ±SD	13.14±2.21		11.39±2.10		2.893	**0.006***
Outcome at 7days	**N**	**%**	**N**	**%**	$X^{2=}$	**0.024***
Still	20	71.4	22	95.7	5.098	
mortality	8	28.6	1	4.3		

DM: Diabetes mellitus, **HTN:** hypertension, **CKD:** chronic kidney disease, **IHD**: ischemic heart disease, X^2**:** Chi square, **UTI:** urinary tract infection, **t**: independent test, **CNS**: central nervous system **SOFA:** Sequential organ failure assessment, **HR:** heart rate**, MAP:** Mean arterial pressure**, ICU:** intensive care unit, X^2**:** chi square, **t:** independent test, **U**: Mann–Whitney U test, *: significant.

Table (3): Demographic, clinical data Diagnosis, and outcome in relation to 15 days survival among control group (n=51).

Variable	Control Group				t	*P* value
	Mortality (N=35)		Improved (N=16)			
Age/years Mean ±SD	58.49±10.12		48.31±9.15		3.562	**0.001***
Comorbidity	**N**	**%**	**N**	**%**	$X^{2=}$ 8.864	**0.015***
DM	10	28.6	3	18.8		
HTN	5	14.3	5	31.3		
HTN,DM	9	25.7	1	6.3		
HTN,IHD	4	11.4	0	0.0		
DM,CKD	1	2.9	1	6.3		
IHD	0	0.0	1	6.3		
Source of sepsis	2	5.7	2	12.5	3.492	0.745
UTI	14	40.0	6	37.5		
Pneumonia	3	8.6	3	18.8		
Soft tissue	7	20.0	3	18.8		
Abdominal sepsis	5	14.3	2	12.5		
Catheter related	3	8.6	0	0.0		
Obstetrics	1	2.9	0	0.0		
CNS infection						

Variable	Diagnosis		*U*	*P* value
APACHE II	28 (16-32)	21 (18-29)	4.446	**<0.001***
Sofa 1st day	14 (10-16)	12 (11-16)	1.073	0.291
Sofa 4th day	16 (8-20)	10 (8-18)	4.370	**<0.001***
Sofa 7th day	20 (4-22)	7.5 (6-22)	4.450	**<0.001***
MAP 1st day	68.7 (61-75.3)	70 (63-74.7)	1.470	0.152
MAP 4th day	73 (69.0-79.3)	75 (70.0-79.7)	1.839	0.076
MAP 7th day	74.3 (70.0-80.7)	75.8 (70.3-81.0)	1.298	0.203
NE 1st day	0.32 (0.24-0.37)	0.28 (0.20-0.35)	2.660	**0.013***
NE 4th day	0.33 (0.02-0.40)	0.05 (0.03-0.07)	5.860	**<0.001***
NE 7th day	0.4 (0.00-0.40)	0 (0-0)	6.310	**<0.001***
HR 1st day	128 (123.0-132.7)	127.7 (121.7-130.7)	0.497	0.623
HR 4th day	117 (112-126)	115 (110.3-118.0)	3.014	**0.005***
HR 7th day	110.7 (101.0-118.7)	105 (100.7-109.7)	4.388	**<0.001***

Variable	Outcome				X^2	*P* value
ICU stays Mean ±SD	12.69±2.60		11.56±2.48		1.480	0.149
Outcome at 7days	**N**	**%**	**N**	**%**	$X^{2=}$ 13.843	**<0.001***
Still	16	45.7	16	100.0		
Mortality	19	54.3	0	0.0		

DM: Diabetes mellitus, **HTN:** hypertension, **CKD:** chronic kidney disease, **IHD**: ischemic heart disease, X^2**:** chi square, **UTI:** urinary tract infection, **t**: independent test, **CNS**: central nervous system, **APACHE II:** Acute physiology and chronic health evaluation II, U: Mann–Whitney U test, **ICU:** intensive care unit, X^2**=** chi square, *: significant.

Table (4): Multiple regression analysis for the parameters affecting mortality rate.

Dependent Variable	β	Std. Error	95% CI		*P* value
			Lower Bound	**Upper Bound**	
Age (years)	59.39	0.96	57.485	61.305	**<0.001***
Comorbidity	2.81	0.22	2.367	3.263	0.941
Source of sepsis	3.01	0.18	2.654	3.371	0.282
APACHE II	25.74	0.49	24.756	26.726	**0.001***
Sofa 1st day	12.50	0.22	12.059	12.953	0.254
Sofa 4th day	11.77	0.42	10.931	12.625	**0.001***
Sofa 7th day	10.66	0.70	9.270	12.064	**0.007***
MAP 1st day	67.36	0.35	66.648	68.077	0.129
NE 1st day	0.27	0.00	0.259	0.291	0.503
HR 1st day	127.19	0.37	126.461	127.934	0.870
MAP 4th day	73.83	0.30	73.219	74.443	**0.044***
NE 4th day	0.13	0.01	0.099	0.163	**0.001***
HR 4th day	108.28	0.95	106.382	110.184	**0.035***
MAP 7th day	74.88	0.33	74.222	75.556	0.212
NE 7th day	0.11	0.01	0.075	0.149	**0.001***
HR 7th day	96.26	1.48	93.301	99.226	0.262
ICU stay	12.32	0.25	11.807	12.835	**<0.001***

APACHE II: Acute physiology and chronic health, **SOFA:** Sequential organ failure assessment, **MAP: Mean arterial pressure, NE, HR:** heart rate, **ICU:** intensive care unit, **CI:** Confidence Interval, *: significant.

Discussion:

This study showed that there was no significant difference among the studied groups regarding APACHE II (P=0.674). While sequential organ failure assessment at 1st, 4th and 7th were significantly decreased among ivabradine group (11.96±2.34, 9.84±2.91, 7.69±4.61) than control group (13.00±1.47, 13.04±4.15, 12.84±6.90) respectively, (P<0.05). An inadequately high resting heart rate as a component of autonomic dysfunction – is a well-known phenomenon in patients with septic shock [8]**.** And in critically ill patients with MODS in general [9]**.** In a study by **Hoke et al., [10]** found that, high heart rate in MODS patients is of prognostic relevance: in a study with 89 patients with MODS of septic and of non-septic origin (APACHE II score ≥ 20), median baseline heart rate was 83 b.p.m. in 28-day survivors and 92 b.p.m. in 28-day non-survivors (p = 0.048; aHR 2.3 for initial heart rate ≥ 90/< 90 b.p.m.). Furthermore, in a study by **Datta et al. [11]** found that the lower SOFA scores in the ivabradine group can be primarily attributed to a lesser vasopressor requirement compared to the control group.

In this study, heart rate at 1st, 4th and 7th were significantly decreased among ivabradine group (126.43±3.81, 100.67±5.11, 83.48±5.33) than control group (127.75±2.30, 115.93±2.84, 108.57±4.51) respectively, (P<0.05). In accordance with our results, in a study **[11],** 60 patients with septic shock and persistent tachycardia (heart rate >95 /minute) were prospectively randomly assigned to receive either standard therapy for septic shock (group S) or standard therapy along with enteral ivabradine (group I) for the initial 96 hours after enrolment. They found that the reduction in heart rate observed in

patients receiving ivabradine in the present study (median difference in AUC –26 /minute) was similar to those reported by previous investigators with intravenous esmolol: –22 /minute [12] - 25 /minute [13] –27 /minute [14] and – 26 /minute [15] Based on the findings of the their study, it appears that ivabradine is of similar efficacy as esmolol, with respect to heart rate reduction in patients with septic shock.

In the current study, there was significant difference among the studied groups regarding outcome at 7 days (P=0.027), 82.4% of ivabradine patients still alive and 17.6% of patients dead. While there was no significant difference among the studied groups regarding 15 days survival (P=0.154). In the same line, in a study done in 2021 [11], it was found that no significant difference in 30-day mortality was detected between the two groups. However, mortality early in the course of illness (with 96 hours of enrolment) was significantly lower in group I (16.6%) compared to group S (40%). Evidence suggests that the pathophysiology of multiple organ dysfunction in the early (within the first 4–5 days) and late phases of sepsis are different–early organ injury being mediated by unregulated inflammatory response and late insult the result of immune paralysis and increased microbial burden [16]. As tachycardia in sepsis is primarily caused by the systemic inflammatory response, it is appropriate that any intervention to control heart rate will have greater impact during the early phase of septic shock.

The current study showed that, the most comorbidity was DM and HTN, DM found in (25.0%) of mortality and in (26.1%) of improved, HTN found in (25.0%) of mortality and in (4.3%) of improved with significant difference among the studied groups. In this concern, the study done in 2021[17] found that AKI is seen in approximately 35% of intensive care patients. The most important causes in more than 50% of AKI cases are sepsis and septic shock. The mortality rate of sepsis-associated AKI varies between 20.9 and 56.13%, depending on the intensity of injury [18 & 19]. Also, a study performed in 2017 demonstrated the beneficial role of using ivabradine in Experimental Sepsis in Twenty-eight golden Syrian hamsters; they found that ivabradine had greater functional capillary density (90 ± 6% of baseline values vs. 71 ± 16%; P < 0.001), erythrocyte velocity in capillaries (87 ± 11% of baseline values vs. 62 ± 14%; P < 0.001), and arteriolar diameter (99 ± 6% of baseline values vs. 91 ± 7%; P = 0.041) at the end of the experiment [20].

In this study, among the ivabradine group, ICU stays was significantly increased among the mortality group (13.14±2.21) than improved group (11.39±2.10). In the same line, in the study done previously 2013 [12] proved that reduction of heart rate by esmolol in septic patients had a 28-day mortality rate of 49.6% vs. 80.5% in the control group (P < .001). Overall survival was higher in the esmolol group. Multivariable Cox regression analysis revealed the esmolol group allocation (hazard ratio [HR], 0.392; 95% CI, 0.261–0.590; P < .001). In contrast with

our results, in a study by **Sobhy et al.** [17]**.** Considering secondary outcomes there were no statistically significant differences between study groups in terms of length of ICU stay and mortality rate (P = 0.390), (P = 1.000) respectively.

In our study, heart rate at 4th and 7th day were significantly increased among mortality (117, 110.7) than improved (115, 105) respectively, (P<0.05). A study done by a group of researchers in 2018 [21] reported that the modify trial is the first randomized trial to assess the effects of ivabradine on patients with MODS and a sinus rhythm ≥90 beats/min. The heart rate reduction observed in patients with MODS (median difference of −9 beats/min after a 4-day treatment) was comparable to the heart rate reduction resulting from orally administered ivabradine in patients with established indications, such as chronic systolic heart failure [Δ = −11 beats/min [22] and chronic coronary artery disease [Δ = −8 beats/min [23]; Δ = −9.9 beats/min [24]**.** It is also similar to the reduction reported for experimental ivabradine indications: Δ = −13.3 beats/min in patients with myocardial infarction who were administered an infusion of ivabradine [25]; Δ = −6.2 beats/min in patients with myocardial infarction complicated with cardiogenic shock who were orally administered ivabradine [26]; and Δ = 10.7 beats/min in patients with acute decompensated systolic heart failure who were orally administered ivabradine [27]**.** Ivabradine infusions were more effective in patients with severe advanced systolic heart failure, who exhibited a heart rate reduction of 20 beats/min [28]**.**

Conclusion

The administration of enteral ivabradine to patients with septic shock and persistent tachycardia resulted in a significant reduction in heart rate and vasopressor requirements, and an improvement in cardiac and microcirculatory function parameters, without an increase in adverse events, increased HR produces adverse impact on myocardium. Our result suggested that ivabradine is an effective, safe, and cost-effective agent for heart rate control in septic shock and our results confirm the potential beneficial effects of Ivabradine administration during septic shock as it improves autonomic control of HR and modulation of HR oscillations but not affects 15 days survival or length of stay in ICU.

References

1. Musialek P, Lei M, Brown HF, Paterson DJ, Casadei B. Nitric oxide can increase heart rate by stimulating the hyperpolarization-activated inward current, I(f). Circ Res. 1997;81:60-8.
2. Werdan K, Schmidt H, Ebelt H, Zorn-Pauly K, Koidl B, Hoke RS, et al. Impaired regulation of cardiac function in sepsis, SIRS, and MODS. Can J Physiol Pharmacol. 2009;87:266-74.
3. Leibovici L, Gafter-Gvili A, Paul M, Almanasreh N, Tacconelli E, Andreassen S, et al. Relative tachycardia in patients with sepsis: an independent risk factor for mortality. Qjm. 2007;100:629-34.
4. Pascual Izco M, Alonso Salinas GL, Sanmartín Fernández M, Del Castillo Carnevalli H, Jiménez Mena M, Camino López A, et al. Clinical Experience with Ivabradine in Acute Heart Failure. Cardiology. 2016;134:372-4.

5. Gallet R, Ternacle J, Damy T, Guendouz S, Bremont C, Seemann A, et al. Hemodynamic effects of Ivabradine in addition to dobutamine in patients with severe systolic dysfunction. Int J Cardiol. 2014;176:450-5.
6. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J. 2005;26:2529-36.
7. De Santis V, Frati G, Greco E, Tritapepe L. Ivabradine: a preliminary observation for a new terapeutic role in patients with multiple organ dysfunction syndrome. Clin Res Cardiol. 2014;103:831-4.
8. Fengler K, Fuernau G, Desch S, Eitel I, Neumann F-J, Olbrich H-G, et al. Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clinical Research in Cardiology. 2015;104:71-8.
9. Sander O, Welters ID, Foëx P, Sear JW. Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications. Crit Care Med. 2005;33:81-8; discussion 241-2.
10. Hoke RS, Müller-Werdan U, Lautenschläger C, Werdan K, Ebelt H. Heart rate as an independent risk factor in patients with multiple organ dysfunction: a prospective, observational study. Clin Res Cardiol. 2012;101:139-47.
11. Datta PK, Rewari V, Ramachandran R, Singh PM, Ray BR, Aravindan A, et al. Effectiveness of enteral ivabradine for heart rate control in septic shock: A randomised controlled trial. Anaesth Intensive Care. 2021;49:366-78.
12. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. Jama. 2013;310:1683-91.
13. Yang S, Liu Z, Yang W, Zhang G, Hou B, Liu J, et al. [Effects of the β-blockers on cardiac protection and hemodynamics in patients with septic shock: a prospective study]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2014;26:714-7.
14. Xinqiang L, Weiping H, Miaoyun W, Wenxin Z, Wenqiang J, Shenglong C, et al. [Esmolol improves clinical outcome and tissue oxygen metabolism in patients with septic shock through controlling heart rate]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2015;27:759-63.
15. Wang Z, Wu Q, Nie X, Guo J, Yang C. Combination therapy with milrinone and esmolol for heart protection in patients with severe sepsis: a prospective, randomized trial. Clin Drug Investig. 2015;35:707-16.
16. Otto GP, Sossdorf M, Claus RA, Rödel J, Menge K, Reinhart K, et al. The late phase of sepsis is characterized by an increased microbiological burden and death rate. Crit Care. 2011;15:R183.
17. Sobhy A, Saleh LA, Shoukry AA. Impact of Ivabradine on renal function in septic patient with early renal impairment. Ain-Shams Journal of Anesthesiology. 2021;13:45.
18. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care. 2007;11:R68.
19. Parmar A, Langenberg C, Wan L, May CN, Bellomo R, Bagshaw SM. Epidemiology of septic acute kidney injury. Curr Drug Targets. 2009;10:1169-78.
20. Miranda ML, Balarini MM, Balthazar DS, Paes LS, Santos MS, Bouskela E. Ivabradine Attenuates the Microcirculatory Derangements Evoked by Experimental Sepsis. Anesthesiology. 2017;126:140-9.
21. Nuding S, Schröder J, Presek P, Wienke A, Müller-Werdan U, Ebelt H, et al. Reducing Elevated Heart Rates in Patients with Multiple Organ Dysfunction Syndrome with The If (Funny Channel Current) Inhibitor Ivabradine. Shock. 2018;49:402-11.
22. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875-85.
23. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a

randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:807-16.
24. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014;371:1091-9.
25. Steg P, Lopez-de-Sà E, Schiele F, Hamon M, Meinertz T, Goicolea J, et al. Safety of intravenous ivabradine in acute ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention: a randomized, placebo-controlled, double-blind, pilot study. Eur Heart J Acute Cardiovasc Care. 2013;2:270-9.
26. Barillà F, Pannarale G, Torromeo C, Paravati V, Acconcia MC, Tanzilli G, et al. Ivabradine in Patients with ST-Elevation Myocardial Infarction Complicated by Cardiogenic Shock: A Preliminary Randomized Prospective Study. Clin Drug Investig. 2016;36:849-56.
27. Sargento L, Satendra M, Longo S, Lousada N, dos Reis RP. Heart rate reduction with ivabradine in patients with acute decompensated systolic heart failure. Am J Cardiovasc Drugs. 2014;14:229-35.
28. De Ferrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart Fail. 2008;10:550-5.

To cite this article: Samir E. Ibrahim, Ehab A. Abdelrahman, Muhammad H. Hagr, Emad F. Rizk. The Outcome of Using First Oral Funny Current Inhibitor Drug in Septic Shock Patients. BMFJ XXX, DOI: 10.21608/bmfj.2024.252286.1965