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Effect of Glucose-Insulin-Potassium Infusion on Hemodynamics in Patients with Septic Shock

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Abstract

BACKGROUND: Glucose-insulin-potassium (GIK) demonstrates a cardioprotective effect by providing metabolic support and anti-inflammatory action, and may be useful in septic myocardial depression.

AIM: The aim of this study was to assess role of GIK infusion in improving hemodynamics in patients with septic shock in addition to its role in myocardial protection and preventing occurrence of sepsis-induced myocardial dysfunction and sepsis-induced arrhythmias.

METHODS: This study was conducted on 75 patients admitted to the Critical Care Department in Cairo University Hospital with the diagnosis of septic shock during the period from January 2019 to December 2019. Patients were divided into two groups; first group was managed according to the last guidelines of surviving sepsis campaign and was subjected to the GIK infusion protocol while second group was managed following the last guidelines of surviving sepsis campaign only without adding GIK infusion.

RESULTS: Patients in the GIK group showed better lactate clearance (50% vs. 46.7%) and less time needed for successful weaning of vasopressors than the control group (3.57±1.16 vs. 3.6±1.45 days) thought not reaching statistical significance. There was no statistically significant difference between both groups regarding development of septic-induced cardiomyopathy (16.7% in the control group vs. 13.3% in the GIK group); however, patients with hypodynamic septic shock showed better improvement in hemodynamic profile in the GIK group. Sepsis-induced arrhythmias occurred more in patients of the control group than in patients of the GIK group with no statistically significant difference between both groups (33.3% vs. 20%, p = 0.243). Few side effects were developed as a result of using GIK infusion protocol.

CONCLUSIONS: GIK may help in improving hemodynamics and weaning of vasopressors in patients with refractory septic shock and those with septic induced cardiomyopathy. The use of GIK was well tolerated with minimal adverse reactions.

Introduction

Sepsis is now defined as

A life-threatening organ dysfunction due to a dysregulated host response to infection. In this new definition, the concept of the non-homeostatic host response to infection is strongly stressed while the term systemic inflammatory response syndrome (SIRS) was been removed. In 2016, a new consensus termed Sepsis-3 removed the concept of SIRS from the sepsis definition and replaced it with the (Sequential Organ Failure Assessment) score [1], [2].

Sepsis-induced organ dysfunction is defined as

The Sequential Organ Failure Assessment (SOFA) score is a simple and objective score that allows for calculation of both the number and the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic) [3]. An acute change in total SOFA score 2 points consequent to infection, reflecting an overall mortality rate of approximately 10%. The baseline SOFA score may be taken as zero unless the patient is known to have a previous comorbidity (e.g., head injury and chronic kidney disease) [1], [2].

In light of this, the present definition, severe sepsis becomes obsolete, as does the term. Screening Tool The qSOFA [3].

A simple bedside score ("qSOFA," for quick SOFA) has been proposed, which incorporates hypotension (systolic blood pressure 100 mmHg), altered mental status and tachypnea (respiratory rate >22 min), the presence of at least two of these criteria strongly predicts the likelihood of poor outcome in patients with clinical suspicion of sepsis.

Septic shock is defined as

A subset of sepsis where underlying circulatory and cellular metabolic abnormalities is profound enough to substantially increase mortality.

Clinical criteria identifying such condition include the need for vasopressors to obtain a (mean arterial blood pressure [MAP] 65 mmHg and an increase

in lactate concentration >2 mmolL, despite adequate fluid resuscitation) [4].

Sepsis is characterized by a complex combination of cardiovascular derangements including vasodilatation, hypovolemia, myocardial depression, and altered microvascular flow. Sepsis-induced cardiomyopathy (SCM) has been recognized as a complication, yet its pathophysiology is only partially understood [4].

It has recently been suggested that SCM can be defined as the intrinsic myocardial systolic and diastolic dysfunction of both the left and right sides of the heart induced by myocardial depressants released from pathogen and host, and global ischemia after peripheral vasodilation, arterial and capillary shunting in septic distributive shock [5].

Reversible myocardial dysfunction of variable severity may occur in as many as 40% of patients with severe sepsis. Myocardial depression often occurs in survivors very early in the septic process, progresses over the first 3 days, and then resolves after 7–10 days [6].

Advanced and highly sensitive echocardiographic studies (including speckle tracking derived longitudinal strain) suggested that some degree of myocardial dysfunction may occur in as many as 20–65% of patients with sepsis which could either be with reduced or preserved ejection fraction [7], [8].

Glucose-insulin-potassium (GIK) has been shown to improve myocardial perfusion and left ventricular function by providing metabolic support and preventing ischemia-related metabolic abnormalities. The cardioprotective effects of GIK may be beneficial in the context of sepsis and are primarily through insulin, resulting in more efficient myocardial metabolism and an anti-inflammatory effect.

Several studies have reported the use of GIK in septic myocardial depression; however, the mechanism of GIK in improving hemodynamics remained unclear [9].

Echocardiography holds a promising potential in the management of septic shock and in the evaluation of the reversible myocardial dysfunction by detecting both ventricular systolic and/or diastolic dysfunctions if present [10].

Aim of the study

We intended in our study to evaluate role of GIK infusion in improving hemodynamics in patients with septic shock and preventing occurrence of sepsis-induced myocardial dysfunction and sepsis-induced arrhythmias.

Patients and Methods

This study is a prospective, randomized, and controlled study and was conducted on 75 patients admitted to the Critical Care Department in Cairo University Hospital with the diagnosis of septic shock during the period from January 2019 to December 2019. Informed consent was obtained from patients or first degree relative.

Inclusion and exclusion criteria

All patients admitted to intensive care unit with septic shock above the age of 18 years were included in the study. Septic shock was identified regarding the third international consensus definition for septic shock (Sepsis-3) [10] as the presence of confirmed or suspected source of infection with a total SOFA score 2 points [11] together with persisting hypotension requiring vasopressors to maintain MAP 65 mmHg and having a serum lactate level >2 mmolL (18 mgdL) despite adequate volume resuscitation.

We excluded from this study; patients who died or transferred to other facility within 48 h, patients below age of 18 years-old, patients refused to be included in our study, patients with volume overload not eligible for fluid resuscitation, patients with chronic severe myocardial dysfunction, patients with uncontrollable hypo or hyperglycemia and hypo or hyperkalemia, and patients with end-stage renal disease.

Echocardiography was performed to all included patients assess myocardial function on inclusion in the study and follow-up within 72 h to detect decline of the left ventricular systolic function (sepsis-induced cardiomyopathy). Echocardiogram was repeated again within 7–10 days in patients who developed septic cardiomyopathy [12].

Patients diagnosed with septic shock were randomized in 11 ratios into two groups each of them was comprised 30 patients:

Group 1 septic shock was managed according to the last guidelines of surviving sepsis campaign 2016 and its update in 2018, and was subjected to the GIK infusion protocol [4].

Group 2 septic shock was managed following the last guidelines of surviving sepsis campaign 2016 and its update in 2018 only without adding GIK infusion protocol [4].

GIK infusion protocol: [9] The intravenous GIK solution consisted of 25% glucose (250 g/L), 50U/L of regular insulin, and 80 mEq/L of KCl. The protocol was to administer GIK intravenously at 1 m/kg/h for the first 72 h and maintain infusion at 40 mL/h as a part of fluid resuscitation protocol until disease improvement or death of the patient [13].

Statistical analysis

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, minimum, and maximum

in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using unpaired t-test (Chan, 2003a) [13]. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is < 5 (Chan, 2003b) [14]. P < 0.05 was considered as statistically significant.

Results

Seventy-five patients with septic shock were initially recruited for this study (Figure 1).

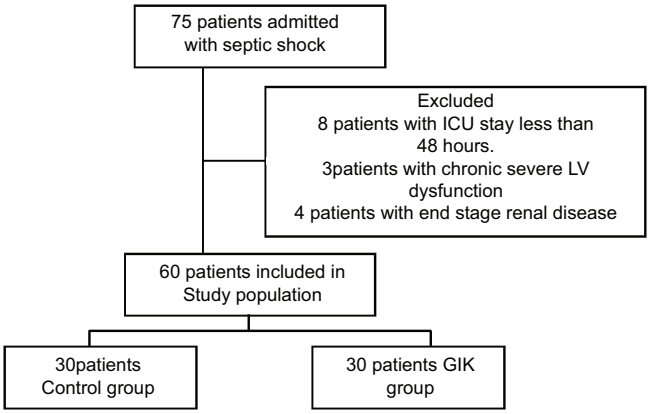

Figure 1: Inclusion and exclusion flow chart

Age

The mean age in the control group was 67.6 ± 13.25 years, while the mean age in the GIK group was 61.8 ± 20.02 years with no statistically significant difference between both groups.

Gender

The control group consisted of 16 (53.3%) females and 14 (46.7%) males while GIK group consisted of 13 (43.3%) females and 17 (46.7%) males. These data were not statistically significant (p = 0.438).

Source of infection

Infection sources are distributed among patients of both groups with no statistically significant differences between them.

APACHE II score

The mean APACHE II score was 19.17 ± 4.32 in the control group with predicted mortality of 33.3 ± 13.12%, while it was 18.731 ± 6.25 in the GIK group with predicted mortality of 32.43 ± 16.76%. There was no statistically significant difference between the two groups (p = 0.756).

Mean arterial pressure on development of septic shock

The MAP on development of septic shock was 52.7 ± 8.59 mmHg in the control group while it was 47.3 ± 10.74 mmHg in the GIK group. The difference in the MAP between both groups was statistically significant (p = 0.036).

Time needed for resolution of shock

Regarding clinical improvement

The clinical improvement (as regard to improved blood pressure, conscious level, and urine output within the first 24 h from the development of shock) was observed in 15 (50%) patients in the control group and 14 (46.7%) patients in the GIK group. There was no statistically significant difference between both groups.

Regarding lactate clearance

Lactate clearance within the first 4 h from the development of septic shock was observed in 14 (46.7%) patients in the control group and 15 (50%) patients in the GIK group. There was no statistically significant difference between both groups.

Time needed for resolution of shock (improvement of tissue perfusion and lactate clearance within the first 4 h of occurrence of shock), lactate clearance (post-resuscitation lactate) is defined as the percentage of lactate cleared over a period of 2–6 h from presentation in the emergency department or intensive care unit with ongoing resuscitation and it was calculated by the equation [(baseline lactate -- serum lactate after 6 h)/baseline lactate) × 100%. Lactate clearance was considered to be achieved in our study by 20% or more reduction from the baseline serum lactate after 4 h.

Mean inotropic score

The mean inotropic score was 40.17–27.11 among patients in the control group and 45 ± 27.44 among patients in the GIK group. There was no statistically significant difference between both groups.

Mean inotropic score which reflected the average doses of vasopressors needed to maintain hemodynamics and calculated as follows:

[dopamine dose (g/kg/min)] + [dobutamine dose (g/kg/min)] + [100× epinephrine dose (g/kg/min)] + [100× norepinephrine dose (gkgmin)].

Mean inotropic score was calculated as the summation of needed doses of vasopressors divided by number of days needed for complete weaning of vasopressors.

Table 1: SOFA score in the first 3 days in patients of the two study group

SOFA score	Group								p-value
	Control				GIK				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
SOFA score 1st	8.67	3.78	4.00	19.00	9.47	2.27	4.00	13.00	0.325
Day SOFA score 2nd day	8.00	3.67	2.0	16.00	8.93	3.07	3.00	14.00	0.290
SOFA score 3rd day	7.83	4.58	1.00	17.00	8.60	4.51	1.00	15.00	0.516

SD: Standard deviation, GIK: Glucose-insulin-potassium, SOFA: Sequential Organ Failure Assessment.

Table 2: ECHO findings among patients of the two study groups

ECHO findings	Group								p-value
	Control (n = 30)				GIK (n = 30)				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
EF (%) 1st day	51.53	10.85	30.00	75.00	52.60	9.68	32.00	70.00	0.689
CO (1st day)	5.69	2.5	2.30	10.00	5.47	2.06	1.90	10.00	0.701
SV (1st day)	53.67	19.89	23.00	100.00	51.17	17.20	15.00	85.00	0.605
CI (1st day)	3.02	1.21	1.30	5.50	2.89	1.23	1.10	5.70	0.689
TAPSE (1st day)	1.71	0.14	1.50	2.20	1.71	0.20	1.10	2.10	1.000
EF (%) 3rd day	51.67	9.19	30.00	70.00	53.17	8.17	35.00	65.00	0.595
CO (3rd day)	5.59	2.14	2.00	12.00	5.36	1.86	2.60	9.80	0.659
SV (3rd day)	57.97	22.80	28.00	120.00	55.57	17.62	25.00	92.00	0.650
CI (3rd day)	3.00	1.08	1.50	6.60	2.82	1.10	1.40	6.00	0.532
TAPSE (3rd day)	1.75	0.19	1.30	2.50	1.74	0.17	1.40	2.20	0.884

EF: Ejection fraction, CO: Cardiac output, SV: Stroke volume, CI: Cardiac index, TAPSE: Tricuspid annular plane systolic excursion, SD: Standard deviation, GIK: Glucose-insulin-potassium.

Time needed for successful weaning of vasopressors

Vasopressors were weaned completely in 3.6 ± 1.45 days in the control group and in 3.57 ± 1.16 days in the GIK group with no statistically significant difference between both groups.

Time needed for successful weaning of vasopressors was defined as the ability of the patient to maintain normal blood pressure for 48 h without any vasopressor support.

Table 3: Ventricular dimensions as shown by ECHO among patients of the two study groups

Ventricular dimensions	Group				p-value
	Control		GIK		
	Count	%	Count	%	
Dimensions (1st day)					
Normal	25	83.3	26	86.7	1
Dilated	5	16.7	4	13.3	
Dimensions (3rd day)					
Normal	27	90.0	28	93.3	1
Dilated	3	10.0	2	6.7	

GIK: Glucose-insulin-potassium.

SOFA score during the first 72 h from inclusion in the study

As shown in Table 1, there was no statistically significant difference among patients of the two study groups regarding improvement in SOFA score after 72 h of management compared with baseline.

Echocardiographic findings to detect cardiac dysfunction and hemodynamic parameters

Table 2 shows echocardiogram (ECHO) findings and hemodynamic parameters in the 1st–3rd days of the study among patients of both groups. There was no statistically significant difference between them.

As shown in Table 3, the left ventricular dimensions were found to be dilated in five patients in the control group and four patients in the GIK group.

These dilated ventricles showed regain of their normal value in only two patients in each group in the follow-up ECHO done after 72 h.

Need for mechanical ventilation

About 24 (80%) and 25 (83.3%) patients needed mechanical ventilation in the control group and GIK group, respectively, with no statistically significant difference between both groups.

Need for renal replacement therapy (RRT)

About 6 (20%) patients needed RRT in the control group but only 3 (10%) patients needed RRT in the GIK group. However, there was no statistically significant difference between both groups.

Development of sepsis-induced cardiomyopathy

Sepsis-induced cardiomyopathy developed in 5 (16.7%) patients in the control group and 4 (13.3%) patients in the GIK group with no statistically significant difference between both groups.

Echocardiographic findings and outcome of patients with SCM

The ECHO findings as regard dimensions and hemodynamics were improved in all the four patients affected with SCM in the GIK group, and in four out of five patients affected with SCM in the control group. Tables 4 and 5 describe the ECHO findings and hemodynamics in patients affected by SCM in the two study groups in the 1st, 3rd, and 7th–10th days of the study.

Development of sepsis-induced arrhythmias

Arrhythmias occurred more in patients of the control group than in patients of the GIK group with no statistically significant difference between both groups (p = 0.243).

Length of hospital stay

There was no statistically significant difference in the length of hospital stay among patients of the two study groups as shown in Table 6.

Mortality

The mortality rate was 70% in patients of the control group and 66.7% in patients of GIK group with no statistically significant difference between both groups.

The mortality cause was progressive shock state in the majority of patients except for three patients in each of the two groups who died due to other causes.

Table 4: ECHO findings and hemodynamics in patients affected by SCM in the two study groups

ECHO findings and hemodynamics	SCM (n = 9)			
	Control (n = 5)		GIK (n = 4)	
	Mean	SD	Mean	SD
EF (%) 1st day	35.00	4.12	37.25	4.57
CO (1st day)	4.88	3.08	4.48	1.89
SV (1st day)	50.20	29.99	37.00	15.98
CI (1st day)	2.66	1.67	2.18	0.83
TAPSE (1st day)	1.60	0.10	1.43	0.24
EF (%) 3rd day	40.00	11.73	41.75	6.24
CO (3rd day)	5.68	3.80	5.83	2.73
SV (3rd day)	57.40	37.00	52.75	27.58
CI (3rd day)	3.20	1.98	2.95	1.16
TAPSE (3rd day)	1.62	0.20	1.55	0.19
EF (7th day)	43.33	11.55	55.00	7.07
CO (7th day)	4.30	1.99	5.70	3.11
SV (7th day)	57.00	23.43	60.00	26.87
CI (7th day)	2.50	0.62	3.05	1.20
TAPSE (7th day)	1.60	0.26	1.75	0.07

GIK: Glucose-insulin-potassium, SCM: Sepsis-induced cardiomyopathy.

Safety parameters assessment in the group received GIK infusion protocol

Hyperglycemia occurred in 14 (46.7%) patients who needed additional insulin infusion to control blood glucose level within range of 140–180 mg/dl; hyperkalemia occurred in 1 (3.33%) patient; hypokalemia occurred in 8 (26.27%) patients who needed additional potassium supplement and no patients developed hypoglycemia (Figure 2).

Table 5: Ventricular dimensions as shown by ECHO in patients affected with SCM in the two study groups

Ventricular dimensions	Group (n = 9)			
	Count	%	Count	%
Dimentions (1st day)				
Normal	0	0	0	0
Dilated	5	100	4	100
Dimensions (3rd day)				
Normal	2	40	2	50
Dilated	3	60	2	50
Dimensions (7th day)				
Normal	4	80	4	100.0
Dilated	1	10	0	0.0

SCM: Sepsis-induced cardiomyopathy.

Table 6: Length of hospital stay in the two study groups

Legnth of hospital stay	Group								p-value
	Control (n = 30)				GIK (n = 30)				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
Legnth of stay	13.03	7.90	4.00	35.00	13.03	8.39	3.00	30.00	1.000

GIK: Glucose-insulin-potassium.

Discussion

In the present study, we tried to assess role of GIK infusion in improving hemodynamics in patients with septic shock and preventing occurrence of sepsis-induced myocardial dysfunction and sepsis-induced arrhythmias. In addition, we tried to assess effect of GIK infusion on patients with septic shock regarding mortality and length of hospital stay. To the best of our knowledge, this study is the first to compare between effects of adding GIK infusion to the management protocol of septic shock and the conventional septic shock management.

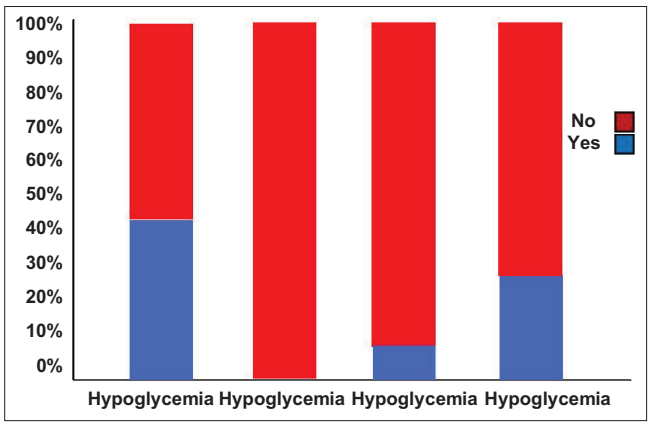

Figure 2:Side effects in the study group of GIK infusion protocol

Incidence of SCM among all our study population was 15% affecting males more than females, 33.3% of patients with SCM had left and right ventricular dysfunction, while 66.7% of them had only left ventricular dysfunction.

These results are in accordance with Sato *et al*. (2016) in their retrospective cohort study conducted on 210 adult patients with sepsis or septic shock admitted to a Japanese tertiary care hospital. They found that SCM developed in 13.8% of patients with sepsis and septic shock with the prevalence rate more in males than in females [4].

In addition, Jeong *et al*. (2018) found that the incidence of SCM was 11.5% in their study conducted on 451 septic patients admitted to intensive care unit in a Korean University Hospital [12].

However, Lu *et al*. (2019) in their study conducted on 93 septic patients, admitted to the critical care department in a Chinese Medical University, found that 51.6% of their patients had septic cardiomyopathy [15].

They found that the highest incidence of cardiac dysfunction caused by septic cardiomyopathy was the left ventricular diastolic dysfunction (43%), followed by the left ventricular systolic cardiomyopathy (25.8%), and the right ventricular systolic dysfunction (11.8%). In addition, they found that different types of cardiomyopathy may occur simultaneously as 8.3% of their patients with septic cardiomyopathy had combined left ventricular systolic, diastolic, and right ventricular dysfunction [15].

This difference in the incidence of SCM between our study and this last one is explained by the high incidence of the left ventricular diastolic dysfunction which was considered alone as a reflection of septic cardiomyopathy according to the Lu *et al*. [15]. However, patients with SCM in our study were diagnosed by a decrease in systolic function of each of the left or right side of the heart or both, as patients with the left ventricular diastolic dysfunction alone caused by other causes than sepsis were not excluded from our study, incidence of septic-induced left ventricular dysfunction alone in our study was 66.7% while it was 43% in the Chinese study [15].

As regard incidence of sepsis-induced arrhythmias, it was found to be 26.7% in our study population in the form of AF (50%), SVT (37.5%), and atrial flutter (12.5%).

Shahreyar *et al*. (2018) in their retrospective study which contained hospital discharge data from the Nationwide Inpatient Sample (NIS) during the period from 2012 to 2018. A total of 30,712,524 NIS hospital discharges (weighted for national estimate) were included in this study, of which 1,756,965 (5.7%) had sepsis. They found that sepsis was associated with a higher prevalence of atrial and ventricular arrhythmias than patients without sepsis (28% vs. 17%) [16].

A retrospective cohort study was performed by Klouwenberg *et al.* (2017) on 1782 patients with sepsis admitted to two tertiary intensive care units in the Netherlands with the purpose of quantifying incidence of AF in patients with septic shock. They found that the incidence of new onset atrial fibrillation was 40% in patients presented with septic shock [17].

The different sample sizes may play a role in this difference in the prevalence of septic-induced arrhythmias between our study and these studies.

The overall mortality rate in all septic shock patients included in our study was 68.3%.

A systematic analysis was performed by de Grooth *et al*. (2018) and included 65 septic shock trials which were published in the period between 2006 and 2018. They found that the control group mortality rates ranged between 13.8 and 84.6%, with a random-effect estimated mean mortality rate of 38.6%. They also found significant heterogeneity among trials ($p < 0.0001$). They referred this heterogeneity among trials to population differences in nutrition and socio-economic status, heterogeneous exclusion criteria, incomplete reporting, between-trial differences in variable definitions, the timing of randomization, and differences in post-randomization cointerventions, and standards of care [11].

In addition, another systematic review and meta-analysis were performed by Vincent *et al*. (2019) and included observational studies in the period between 2005 and 2018 for that reported on the frequency and mortality of septic shock [18].

They found that the mean mortality in the ICU was 37.3% among patients with septic shock in the included articles with the high level of heterogeneity observed in this review. They assumed this high level of heterogeneity to the variability in defining and applying the diagnostic criteria, as well as differences in treatment and care across settings and countries. However, they found that using mortality rates from patients diagnosed with Sepsis-3 definitions were considered a potential source of heterogeneity as ICU mortality estimates increased to 51.9% when septic shock was diagnosed using Sepsis-3 criteria.

This difference in mortality rates between our study and these studies may be due to the variable causes of heterogeneity that was mentioned in regarding evaluating role of GIK in improving hemodynamics in patients with septic shock, we found that patients who received GIK infusion protocol showed significantly lower MAP, on occurrence of septic shock, than the control group which was reflected by the increased inotropic score in the GIK group. Despite these results, patients in the GIK group showed better lactate clearance and less time needed for successful weaning of vasopressors than the control group though not reaching statistical significance.

These findings are supported by Slob *et al*. (2017) in their retrospective study applied on 85 patients with shock state (83.5% of the patients had septic shock, while 11.8% of patients had cardiogenic shock) at a tertiary care teaching hospital in the United Kingdom where patients who had not responded to conventional catecholamine therapy, received GIK infusion [19].

They found a trend of improved lactate levels with reductions in catecholamine dosing in patients who survived until 72 h [19].

Similarly, Kim *et al*. (2016) in their study conducted on 45 patients with septic shock, found that GIK increased MAP and tended to decrease HR particularly in patients with hypodynamic septic shock [20].

Furthermore, Hamdulay *et al*. (2006) described two cases of septic shock which were resistant to vasopressors and responded to high-dose GIK infusions they found that hemodynamics improved markedly with GIK infusions allowing successful weaning of vasopressors [9].

There was no statistically significant difference between GIK group and control group regarding development of SCM; however, we found that patients with hypodynamic septic shock showed better improvement in hemodynamic profile, including stroke volume, cardiac output, and cardiac index in the GIK group than in the control group.

This finding is supported by Kim *et al*. (2016) as they found that GIK helps to improve cardiac output and other echocardiographic parameters in eight out of 12 patients affected with hypodynamic septic shock, so they suggested that GIK may be effective in septic shock exacerbated by septic myocardial depression [20].

Similarly, Bassi *et al*. (2013) in their review article which included few studies that addressed role of GIK solution in management of refractory shock, reported that GIK seems to improve cardiac output and cardiac index in patients with hypodynamic inflammatory shock [21].

Regarding the need for RRT, we found that number of patients who needed RRT was 6 (20%) in the control group which was double that of patients in the GIK group where only 3 (10%) patients needed RRT, with no statistically significant difference between both groups. This finding may be related to the renal protective role of insulin being a major component of GIK.

These results are in accordance with Thomas *et al*. (2007) in their systematic review that involved five studies conducted in intensive care unit settings. They found that intensive insulin therapy reduced the incidence of dialysis requirement by 35% [22].

In addition, a meta-analysis that involved two large, prospective, randomized, and controlled trials was performed by Schetz *et al*. (2008). They found that intensive insulin therapy targeting normoglycemia protected the kidney of critically ill patients and decreased need for RRT [23].

As regard to length of hospital stay and mortality, we did not find any statistically significant difference between GIK group and control group.

These results are supported by Kim *et al*. (2016) who reported that there was no significant benefit in mortality among patients with hypodynamic septic shock who received GIK infusion protocol despite the short-term hemodynamic improvement in that group [20].

In addition, Michael *et al*. (2009) performed a systematic review and meta-analysis of randomized controlled trials comparing GIK treatment with standard care or placebo in critically ill adult patients whatever their diagnoses. They found that there is no mortality benefit to GIK infusion in critically ill patients [24].

Finally, and as regard to assessment of safety parameters of GIK solution, we found that GIK solution was well tolerated by the included patients and few side effects were developed; hyperglycemia in 14 (46.7%), hypokalemia in 8 (26.6%) while hyperkalemia occurred in only 1 (3.33%) patient. These side effects were adequately managed and did not mandate discontinuation of GIK infusion protocol.

Similarly, Kim *et al*. (2016) found that the use of GIK solution was well tolerated with minimal adverse drug reactions [20].

In addition, Slob *et al*. (2017) reported that high-dose GIK can be safely used in critically ill patients, though blood glucose and potassium levels must be monitored frequently [19].

Conclusion

- GIK may help in improving hemodynamics and weaning of vasopressors in patients with refractory septic shock and those with septic induced cardiomyopathy
- The use of GIK may help to decrease incidence of arrhythmias in patients with septic shock
- The use of GIK in patients with septic shock may help to decrease incidence of AKI and need for dialysis
- The use of GIK is well tolerated with minimal adverse reactions.

Recommendations

We recommend the use of GIK solution in patients of septic shock who are vasopressor resistant and those with septic induced cardiomyopathy as GIK may help in improving hemodynamics and weaning of vasopressors in these patients.

Further studies are required to demonstrate the role of GIK in septic shock.

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