Biolife 5(2):216-223
AN INTERNATIONAL QUARTERLY JOURNAL OF BIOLOGY & LIFE SCIENCES
ISSN (online): 2320-4257
www.biolifejournals.com
BIOLIFE RESEARCH ARTICLE

Impact of combined low dose norepinephrine and simvastatin on sepsis induced acute Kidney injury in critically ill patients

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ABSTRACT

Background: The role of statins in sepsis patients with acute kidney injury (AKI) is still unclear. This study was done to evaluate the effects of oral Simvastatin and low dose intravenous norepinephrine as an adjunctive therapy in early acute kidney injury associated with sepsis.
Methods: we enrolled 60 patients with severe sepsis had early diagnosed acute kidney injury with high plasma NGAL* test. They were randomly assigned to 2 groups; Group A (n =30) received oral Simvastatin 80 mg/day and low dose intravenous norepinephrine (2 to 4 µg /min) plus conventional sepsis treatment., Group B (n =30) received only conventional sepsis treatment. Then both were followed by: CRP*, PCT*, SOFA score* monitoring, RIFLE criteria* and Need for organ supportive measures, Length of ICU stay and 28-day Mortality.
Results: Group A showed no any statistically significant differences except a significant reduction in Mean SOFA score on day 2 and 3 only (p value = 0.012 and 0.013 respectively) and in need for vasopressor (p value = 0.004).
Conclusions: Simvastatin and low dose norepinephrine did not show any improvement in patients with sepsis associated AKI.
Abb. NGAL: Neutrophil gelatinase-associated lipocalin, CRP:C-reactive protein, PCT: Procalcitonin, SOFA score: Sequential organ failure assessment score, RIFLE criteria: Risk, Injury, and Failure, Loss and End-stage renal disease.

Keywords: Critical; Sepsis; AKI; Norepinephrine; simvastatin

INTRODUCTION

Sepsis as a life-threatening syndrome caused by a dysregulated host response to infection.[1-3] The term severe sepsis is no longer used since 2016.[1, 4, 5] sepsis and septic shock definitions include patients with evidence of tissue hypoperfusion and organ dysfunction.

Acute kidney injury (AKI) is a common and serious complication of sepsis in intensive care unit (ICU) patients, particularly in the elderly and it is associated with a high mortality rates.[6-8] The pathophysiology of AKI during sepsis is complex and multifactorial and involves changes of renal hemodynamic, renal parenchymal inflammation and metabolic response of tubular cells to changes in the local environment.[9]

The exact pathophysiology in septic AKI may lead to expression of specific serum and urine biomarkers. Neutrophil gelatinase-associated lipocalin (NGAL) has been validated as an early biomarker of AKI.[10, 11] Haase et al. confirmed the predictive and prognostic value of NGAL as an early biomarker for AKI in a meta-analysis involving 19 studies (> 2,500 patients).[12] Induction of this biomarker after kidney injury precedes the elevation of old markers for kidney damage e.g. serum creatinine.[13, 14]

Acute Dialysis Quality Initiative (ADQI) in 2004 defined the first definition and staging of AKI by

How to Site This Article:
Tayseer Zaytoun, Mohamed Megahed, Sherif Abdelfattah, Mahmoud El-Sabbagh and Islam Ahmed (2017). Impact of combined low dose norepinephrine and simvastatin on sepsis induced acute Kidney injury in critically ill patients. *Biolife*. 5(2), pp 216-223.

DOI: 10.5281/zenodo.7364238
Received: 6 April 2017;
Accepted; 23 May 2017;
Available online : 4 June 2017

presenting RIFLE criteria (Risk, Injury, and Failure, Loss and End-stage renal disease) for kidney injury.[15] The RIFLE criteria staged AKI by elevation in serum creatinine from baseline, by decrease in estimated glomerular filtration rate, and by diminished urine output.

Low doses of norepinephrine (NE) (2 to 4 µg /min) may decrease vascular resistance with increased renal blood flow.[16] In human studies, norepinephrine has been shown to increase creatinine clearance and urine output in septic shock[17, 18] and to decrease the renal resistance index assessed by Doppler ultrasonography.[19]

Statins have been shown to act on several steps in sepsis: the generation of Proinflammatory cytokines (Interleukin-6, Interleukin-8, and Tumor necrosis factor-α), modulation of leukocyte and monocyte functions, and reduction of oxidative stress as well as improvement in endothelial function and platelet activity. Simvastatin have pleiotropic effects independent of lipid lowering.[19, 20] In one trial, simvastatin reduced the systemic response to endotoxin administration and decreased expression of Toll-like receptors that hold a key early role in sepsis. [21, 22]

In this study we investigated the effect of short term oral Simvastatin and low dose intravenous NE as an adjunctive therapy in early sepsis induced acute kidney injury.

PATIENTS AND METHODS

We prospectively enrolled sixty patients with early sepsis who had early diagnosed acute kidney injury with high plasma NGAL test; they were randomly selected from patients with severe sepsis who admitted to the department of Critical Care Medicine at the Alexandria Main University Hospital; from august 2015 to august 2016.

Inclusion Criteria:

1. Informed consent given by the patient or immediate relative (first degree).
2. Any adult patient with severe sepsis and high plasma NGAL.

Exclusion Criteria:

1. Individuals less than 18 years of age.
2. Patients already on statin or have history to allergy or intolerance to statins.
3. Pregnant and lactating mothers.
4. Active liver disease patient (ALT >3 times above the upper limit of normal and Hyperbilirubinemia)
5. Elevated creatine phosphokinase (CPK) (>3 times the upper limit of normal)
6. Chronic kidney disease (CKD) patient.
7. Polytrauma, burn, ileus and rheumatologic diseases patient.
8. Immunocompromised patient.
9. Concurrent treatment with any drug with known interaction with simvastatin.

After the approval of critical care department ethical committee had obtained, the Patients who met the inclusion criteria were randomized into the study. Studied patients (n=60) were divided into 2 equal groups (each consists of 30 patients) on a simple randomization pattern on basis of odd and even number.

Group A (Intervention): Patients received Simvastatin 80 mg orally and low dose NE (2 to 4 µg /min) daily plus conventional sepsis treatment.

Group B (Control): Patient received only conventional sepsis treatment.

All patients were followed-up from time of enrollment till the day of discharge or demise and evaluated by:

- Demographic data and full history including: age, gender, history of DM, HTN, medications, and previous ICU admission.
- Complete physical examination including vital signs, chest, cardiac, abdomen and extremities examination.
- Investigations:
  Radiological: Chest, abdominal, extremity radiography, abdominal ultrasonography, computed tomography of the abdomen to identify the source of sepsis.

Laboratory: Complete blood count with differential, Red cell distribution width (RDW) and Mean platelet volume (MPV), Coagulation studies (e.g., prothrombin time [PT], activated partial thromboplastin time [aPTT]), Blood chemistry (e.g., sodium, chloride, magnesium, phosphate, glucose), Renal and hepatic function tests (e.g., creatinine, blood urea nitrogen, bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin, lipase), CPK: Creatine phosphokinase, ABG and Pao_2/ Fio_2. These routine Labs were withdrawn on study day 1 and subsequently there after every other day until ICU discharge or demise. CRP (C-reactive protein) and PCT Procalcitonin done at day 1 and day 4.

Microbiological: Sputum, Blood and urine cultures, cultures of secretions and tissue, Gram stain and urine analysis done prior to antibiotic administration or after discontinuation of antibiotic for 48 hrs.

- APACHE II score (Acute Physiology and Chronic Health Evaluation II) was evaluated on study day 1.
- SOFA score (Sequential Organ Failure Assessment) was evaluated on study day 1 and serially every day until ICU discharge or demise.
- RIFLE criteria were evaluated daily.
- Clinical data: Length of ICU stays, duration of hospital stays, mortality, need for organ supportive measures (Vasopressors, Mechanical ventilation MV and/or Hemodialysis HD).

RESULTS

The baseline clinical characteristics and demographic data of the 2 groups in this study were found to be comparable regarding age, gender, risk factors, source of sepsis, organism and vital signs.

Chest infections were the most common source of sepsis in both groups (Table-1).

The mean Plasma NGAL level of both groups elevated above normal range (48-390 ng/ ml) was no significant difference (*p* value = 0.211) (Table-2).

Table-1. Demographic and clinical data of the two studied groups.

	Group A	Group B	*P* value
Age	47.6±14.44	53.3±15	0.070
Gender	%	%	0.500
• Male	17 (56.7)	17(56.7)	
• female	13 (43.3)	13(43.3)	
Source of sepsis:	%	%	0.088
• Chest	80.0	70.0	
• Abdomen	0.0	20.0	
• Soft tissue	10.0	6.7	
• UTI	6.7	0.0	
• CNS	3.3	3.3	
Organism:	%	%	0.551
• No Growth	36.3	47.8	
• Gram -ve	50.5	38.5	
• Gram +ve	13.2	13.3	
Risk factors:	%	%	
• CVS	60	43.3	0.08
• Previous ICU	30.0	13.3	0.06
• IHD	20.0	13.3	0.25
• DM	26.7	30.0	0.39
• Bed sore	10.0	13.3	0.35
• COPD	10.0	20.0	0.14
• AF	23.3	23.3	0.50
• ARDS	6.7	10.0	0.32

*χ2: Chi square test for comparing between the two groups in all variable except age measured by Student t test. MC: Monte Carlo for Chi square test and Student t test for comparing between the two groups. Significant between periods was done using Marginal Homogeneity Test. *: Statistically significant at p ≤ 0.05. UTI: urinary tract infection, CNS: central nervous system, CVS: cerebrovascular stroke, IHD: Ischemic heart disease, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, AF: atrial fibrillation, ARDS: acute respiratory distress syndrome.*

Table-2. Mean ± SD of Plasma NGAL level in both group:

	Group A	Group B	*P* value
Plasma NGAL	559.6±105	596.8±110.8	0.211

*Student t test for comparing between the two groups MC: Monte Carlo for Student t test for comparing between the two groups Significant between periods was done using Marginal Homogeneity Test. *: Statistically significant at p ≤ 0.05. NGAL: Neutrophil gelatinase-associated lipocalin*

The effect of Simvastatin and low dose NE was determined by C-reactive protein **(**CRP) level and Procalcitonin (PCT). The mean CRP level of both groups was compared at predetermined follow-up days (Study day 1 and 4). The mean level of CRP in day 1 and day 4 in both groups elevated above normal range (≤ 6mg/l) with non-significantly difference (*p* value = 0.11, 0.138 respectively). The mean level of PCT in day 1 and day 4 in both groups elevated above normal range (≤ 0.5ng/ ml) with non-significantly difference (*p* value = 0.497, 0.145 respectively) (Table 3).

Table-3. Mean ± SD of C-reactive protein and procalcitonin levels at day 1 and day 4.

CRP	**Group A**	**Group B**	**P value**
1st day	57.1±38.57	68.9±72	0.11
4th day	21.3±23.83	30.1±36.81	0.138
PCT	**Group A**	**Group B**	**P value**
1st day	1.7±1.52	1.7±1.29	0.497
4th day	0.7±0.82	1.2±2.46	0.145

Student t test for comparing between the two groups. MC: Monte Carlo for Student t test for comparing between the two groups Significant between periods was done using Marginal Homogeneity Test. Statistically significant at p ≤ 0.05. CRP: C-reactive protein. PCT: Procalcitonin.

Evaluation of severity of illness during ICU stays using APACHE II score, SOFA score and RIFLE criteria. When comparing between the two groups on admission, there was no significant difference in APACHE II (*p* value = 0.442) (Table 4). When comparing the initial SOFA score between the two groups on admission; it showed no significant difference (*p* value = 0.14) between both group. During the early hospital course there was significant difference between both groups in favor of group A, as indicated by Mean SOFA in day 2 and day 3 (*p* value = 0.012 and 0.013 respectively), but with no significant difference between both groups as indicated by Mean SOFA in day 4 to day 10 (*p* value = 0.133, 0.150, 0.060 and 0.159 respectively) (Table-5).

Table-4. Mean ±SD of APACHE II score in both groups at time of admission.

	Group A	Group B	P value
APACHE II	22.0±6.70	21.8±7.07	0.442

Student t test for comparing between the two groups MC: Monte Carlo for Student t test for comparing between the two groups Significant between periods was done using Marginal Homogeneity Test. Statistically significant at p ≤ 0.05. APACHE II: Acute Physiology and Chronic Health Evaluation II

When comparing the mean values of RIFLE criteria during hospital stay, there was no significant differences between both group in the first 10 days of the study (*p* value = 0.407, 0.210, 0.214, 0.500, 0.075, 0.280 and 0.337 respectively) (Table-6) (Figure-1).

Table-5. Mean ± SD of SOFA score in both groups.

SOFA score	Group A	Group B	P value
1st day	7.2±2.75	8.3±2.05	0.14
2nd day	8.6±2.25	10.3±3.05	0.011*
3rd day	9.5±2.85	11.4±3.53	0.013*
4th day	10.1±3.30	11.2±4.21	0.133
5th day	10.2±3.42	11.4±5.08	0.150
6th day	9.9±5.24	12.3±6.45	0.060
10 day	9.2±4.46	11.2±5.02	0.159

*Student t test for comparing between the two groups. MC: Monte Carlo for Student t test for comparing between the two groups Significant between periods was done using Marginal Homogeneity Test. *: Statistically significant at p ≤ 0.05. SOFA: sequential organ failure assesment.*

Table-6. Mean ±SD of RIFLE criteria in both groups

RIFLE criteria	Group A	Group B	P value
1st day	1.2±0.63	1.3±0.45	0.407
2nd day	1.8±0.71	1.7±0.55	0.210
3rd day	2.2±0.89	2.0±0.72	0.214
4th day	2.7±0.84	2.7±0.84	0.500
5th day	2.7±0.83	3.0±0.76	0.075
6th day	3.0±0.81	3.2±0.95	0.280
10 day	2.8±0.75	3.0±1.04	0.337

Student t test for comparing between the two groups. MC: Monte Carlo for Student t test for comparing between the two groups Significant between periods was done using Marginal Homogeneity Test. Statistically significant at p ≤ 0.05. RIFLE: Risk, Injury, and Failure, Loss and End-stage renal disease.

When comparing both groups regarding the need for organ supportive measures we found that significant decrease in need for vasopressors (*p* value = 0.010) in favor of group A, but with non-significantly differences in both group in need for mechanical ventilation (M.V.) and need for acute hemodialysis (H.D.) (*p* value = 0.187and 0.306 respectively) (Table-7) (Figure-2).

Regarding the secondary outcomes, we founded that the range of length of hospital stay was (6-40) days with median 11.50 for group A versus (7-40) with median 9.5 days for group B (*p* value= 0.351); which signifies a statistically no significant reduction in length of hospital stay. The range of length of stay in the ICU was (6-33) days with median 10.0 for group A versus (7-40) days with median 9.0 for group B (*p* value= 0.094); which signifies a statistically no significant reduction in length of ICU stay (Table-8). When we compared the 28-day mortality, it was less in group A (56.7%) compared to the group B (60%); however, this difference was not statistically significant (*p* value = 0.399).

Table-.7. The need for organ supportive measures during the study in the 2 studied groups.

	Group A	Group B	P value
Need for vasopressor	18 (60%)	26 (86.7%)	0.010*
Need for MV	28 (93.3%)	25 (83.3%)	0.187
Need for HD	15 (50%)	13 (43.3%)	0.306

*χ^2: Chi square test for comparing between the two groups. MC: Monte Carlo for Chi square test for comparing between the two groups. Significant between periods was done using Marginal Homogeneity Test. *: Statistically significant at p ≤ 0.05. MV: Mechanical ventilation. HD: Hemodialysis.*

Table-8. The median and range of length of ICU and hospital stay of both groups

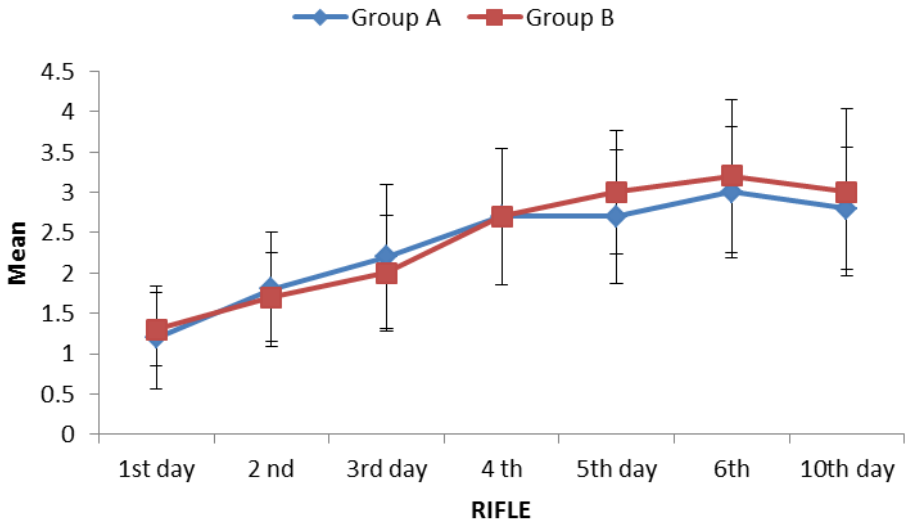
	Group A	Group B	P
Length of ICU stay			
Range	(6-33)	(7-40)	
Median	10.0	9.0	0.094
Length of hospital stay			
Range	(6-40)	(7-40)	
Median	11.50	9.5	0.351

Student t test for comparing between the two groups. MC: Monte Carlo for Student t test for comparing between the two groups Significant between periods was done using Marginal Homogeneity Test. Statistically significant at p ≤ 0.05.

DISCUSSION

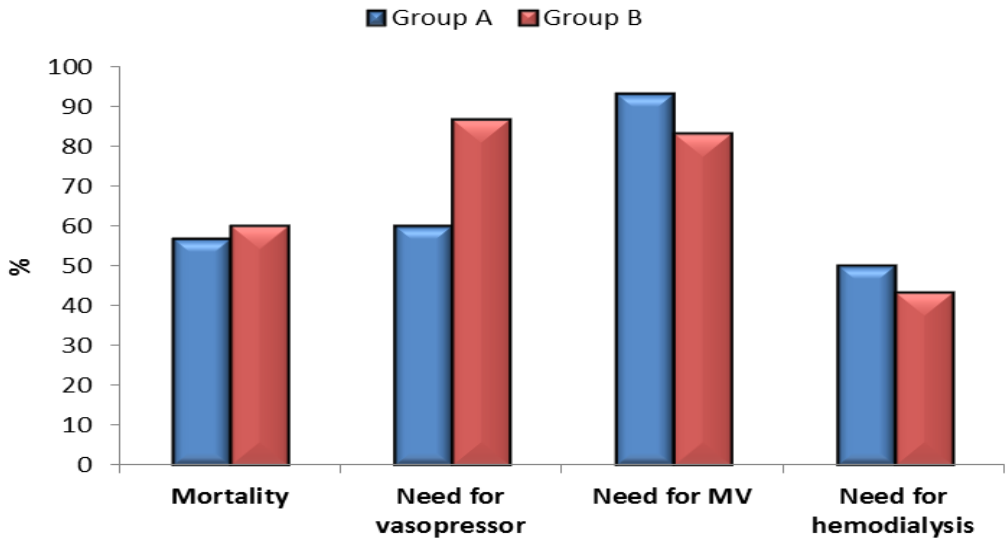
Sepsis associated AKI is induced by an abrupt worsening in renal function after exposure to sepsis. The serum creatinine level may fail to reflect this deterioration in the first 24 to 48 hours because serum creatinine concentrations may not be changed until about 50% of kidney function has already been lost and a steady state of serum creatinine nictitate several days to be reached.[23, 24] So, plasma NGAL is usually used as early biomarker for detection of AKI.[12]

Figure-1. Mean ±SD of RIFLE Criteria



Comparing the mean values of RIFLE criteria during hospital stay, there was no significant differences between both group in the first 10 days of the study (p value = 0.407, 0.210, 0.214, 0.500, 0.075, 0.280 and 0.337 respectively).
****RIFLE:** Risk, Injury, and Failure, Loss and End-stage renal disease.*

Figure-2. The need for organ supportive measures



Comparing both groups regarding the need for organ supportive measures we found that significant decrease in need for vasopressors (p value = 0.010) in favor of group A, but with non-significantly differences in both group in need for mechanical ventilation (MV) and need for acute hemodialysis (HD) (p value = 0.187and 0.306 respectively).

We assessed renal function by measuring plasma NGAL at time of enrollment then, the serum levels of creatinine, blood urea nitrogen and urine output daily in both groups. Unfortunately, in our study there were no significant differences in these variables between both groups. When we compared the progression of AKI in both group by mean RIFLE criteria during hospital stay, there was no significant differences between both groups.

Almog Y, et al.[25] and Merx MW, et al. [26] Simvastatin has an adequate safety profile in septic patients. Hideo Yasuda , et al.,[27] demonstrated that simvastatin had a beneficial effect on sepsis-induced AKI. A lot of studies have been shown beneficial effects of statins in other kidney diseases as ischemia-reperfusion injury, chronic kidney disease and renal transplantation.[20, 28, 29]

Simon L et al.[30] had shown that C-reactive protein as markers of bacterial infection in critically ill children at

onset of systemic inflammatory response syndrome. In our study we had examined the anti-inflammatory effect of simvastatin as guided by measuring serum levels of CRP and PCT at study day 1 and 4 which reflects the effect of simvastatin on drivers of sepsis. We had found that; the mean level of CRP and PCT in day 1 was elevated above normal range 6 mg/L and ≤ 0.5ng/ml respectively), this was explained by sepsis. The mean level CRP and PCT in day 4 decreased in both groups and this reduction was statistically not significant between the two groups (*p* value = 0.138, 0.145).

Jian-junli, et al., [31] had demonstrated a significant plasma CRP reduction in the first 2 weeks of simvastatin treatment in in patients with hypercholesterolemia. Arnaud C, et al., had demonstrated that statins have direct anti-inflammatory effects on hepatocytes by reducing the process of IL-6-induced CRP production. [32]. Mihai Mărginean, et al., had demonstrated A significant PCT reduction with simvastatin treatment group during Comparing the anti-inflammatory effects of simvastatin and rosuvastatin by measuring IL-1β, IL-6 and TNF-α levels.[33]

Novack and colleagues [34] showed that treatment with simvastatin reduce cytokine levels at 72 hours. Hideo Yasuda, et al. [27] found that simvastatin inhibits serum TNF-alpha elevation in animal study. Merx MW et al, [35] demonstrated that Simvastatin, which is well established in the treatment of lipid disorders and coronary artery disease, might have the additional potential of being an effective agent in sepsis treatment.

We did not reach statistical significance in decreasing CRP, and PCT levels among the patients on simvastatin therapy. But this may be due to short duration of our study as a statin treatment need duration of 8 to 12 weeks to achieve pleotropic effects [36-38], but in animal's study, simvastatin improved survival in short period. [27, 34, 35, 38]

In addition, we had examined the effect of early Simvastatin and low dose NE therapy on reducing the severity of sepsis during early first three days of sepsis as indicated by comparing SOFA score during ICU stay as follows: The initial SOFA score between the two groups on admission showed no significant difference between both groups (*p* value = 0. 14). During the early hospital course (day 2 and day 3) there was a significant difference between both groups in favor of group A, as indicated by Mean SOFA (*p* value = 0.012 and 0.013 respectively).

Regarding the effect of Simvastatin and low dose NE on clinical course, when comparing both groups, we found that Group A (the Simvastatin and low dose NE group) exhibited significant decrease in need for vasopressors (p value = 0.010) on the other hand there was no significant decrease in the need for acute hemodialysis (*p value* = 0.306) or need for mechanical ventilation (p value = 0.187).

In relation to mortality, we found that a statistically no significant reduction in 28-day mortality in group A: The 28-day mortality was less in the Simvastatin and low dose NE group (56.7%) compared to the control group B (60%) (*p* value = 0.399).

Liappis AP, et al. [39] reported that statins reduce both overall and attributable mortality in patients with bacteremia. Almog Y , et al. [25] revealed that prior statin therapy associated with a reduction of severe sepsis and intensive care unit admission. Merx MW et al. [26] Also In animals, simvastatin improved survival. [35]

CONCLUSION

In our study, Simvastatin and low dose norepinephrine did not prevent the progression of sepsis induced acute kidney injury in critically ill patients with severe sepsis as we didn't find any significant difference between the two groups of study. Further studies on a larger scale may show statistically and clinically significant differences and support previous published clinical data and animal studies about their role.

Ethics:

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria University and the department of critical care, Informed consents for participating and publishing were taken from patients or the next of kin after approval by critical care department committee.

Trial Registration:

IRB No: 00007555 FWA No: 00015712 The Ethics Committee of the faculty of medicine Alexandria University.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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