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The impact of early norepinephrine administration on outcomes of patients with sepsis induced hypotension, randomized controlled prospective study

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Abstract
Background: Hypovolemia and reduced vascular tone have a role in determining the severity of hypotension in septic shock. The risk of fluid overload is presented as common complication during septic shock resuscitation. The study aimed to investigate the effect of early norepinephrine administration on outcomes of patients with sepsis induced hypotension.
Methods: This study was performed on 64 patients diagnosed with sepsis. The patients were randomly allocated into two groups,
Group A: Received 30ml /kg ringer's lactate solution after first presentation then norepinephrine was added when persistent mean arterial pressure was still lower than mmHg despite adequate fluid resuscitation.
Group B: Received 30ml /kg ringer's lactate solution after first presentation combined with norepinephrine infusion (0.05 mic/kg/min).
Results: Time to reach MAP ≥ 65 mmHg showed statistically significant decrease in group B compared with group A. Mean arterial blood pressure in group B Showed statistically significant increase compared with group A. In group B: there were statistically significant decrease in heart rate changes compared with group A. There was statistically significant decrease in group B compared with group A in volume of intravenous fluid administered, quantity and dose of norepinephrine during 1st day, duration of norepinephrine, total leukocyte count, blood urea, serum creatinine and serum lactate and 30 days mortality. Urine output showed statistically significant increase in group B compared with group A at 1h, 6h, 12h and 24h follow up.
Conclusion: Norepinephrine as part of initial resuscitation of sepsis induced hypotension result in decreased time to reach target MAP, decrease IV fluid requirement, lowers blood lactate levels, and decreases mortality rate.

Keywords: Sepsis, hypotension, norepinephrine, early infusion, fluid resuscitation

Introduction
One of the most serious problems in the intensive care unit is septic shock (ICU) [1]. Septic shock has been identified as the leading cause of morbidity and mortality in critically ill patients over the past few decades, accounting for 30% to 40% of ICU mortality [2]. Septic shock is defined as sepsis combined with hypotension which is still persistent. This requires vasopressors therapy despite sufficient volume resuscitation to achieve the following targets; mean arterial pressure (MAP) greater than or equal to 65 mmHg, having serum lactate level lower than 2 mmol/L (18 mg/dL) [3].
Hypovolemia and reduced vascular tone have a role in determining the severity of hypotension in septic shock [4]. Organ blood flow is physiologically dependent on perfusion pressure when mean arterial pressure (MAP) drops below a particular threshold level. Early on, fluid resuscitation and vasopressors are used in combination therapy to treat hypovolemia and enhance vascular tone [5]. Norepinephrine (NE) is considered as a first vasopressor line which retrieve vascular tone to maintain organ perfusion [6-7]. The risk of fluid overload created by large quantity of fluid administration, is presented as common complication during septic shock resuscitation [8]. After the early phase, only fifty percent of patients respond to fluid administration, meaning that fluid treatment cannot boost cardiac output (CO) [9].

The current data indicates that the time from the onset of septic shock to the initiation of norepinephrine administration is a significant survival predictor; however, a suggestion for the optimal time to provide norepinephrine support was not explicitly expressed [5]. We hypothesized that early administration of nor epinephrine at start of sepsis induced hypotension could achieve hemodynamic stability and accelerate shock management. The researchers conducted this randomized controlled trial to investigate the impact of early norepinephrine administration on outcomes of patients with sepsis induced hypotension.

Patients and methods

For 64 sepsis patients admitted to the ICU at Tanta university Hospitals in Egypt, this prospective randomised controlled comparative study was conducted. From May 2021 until January 2023, the Institutional Ethical Committee's clearance was prospectively obtained using ID: 34643/4/21. The study was verified by Clinical Trials.gov with ClinicalTrials.gov ID: NCT05774054. The patient's relative was requested for their informed consent. All patient information was kept private. Secret codes and patient-specific private files were used to protect secrecy. All information was gathered only for the current study.

If the patients were adult patients, aged 18 to 60, they were included in the analysis. These eligible individuals met the diagnostic requirements for sepsis according to Surviving Sepsis Campaign, which include the presence of an infection that is "documented or suspected," together with systemic infection manifestations and hypoperfusion-related symptoms. The signs of organ hypoperfusion was defined as reduced urine output lower than 0.5mL/kg/hr, disturbed conscious level, prolonged capillary refill time and hypotension with MAP lower than 65 mmHg.

Patients who met the sepsis diagnostic criteria and had Acute cerebral vascular event, active cardiac condition including acute coronary syndrome, active cardiac arrhythmias, valvular heart diseases, hypotension suspected to be due to another cause and comorbidities, status asthmatics, active hemorrhage, pregnancy, burn injury, indication of emergency surgery, end -stage cancer and those who declined to take part in the study were omitted.

The eligible patients were enrolled in the study and randomly allocated into two groups. The computer-generated software of randomization was used and this randomization manner was presented into closed sealed opaque envelops:

- **Group A**: received 30ml /kg of predicted body weight ringer's lactate solution after first presentation within the first 3hr of resuscitation then norepinephrine was added when persistent mean arterial pressure (MAP) remains still lower 65 mmHg despite adequate fluid resuscitation.
- **Group B**: received 30ml /kg of predicted body weight ringer's lactate solution after first presentation combined with norepinephrine infusion starting at 0.05 mic/kg/min and increased gradually up to 0.5 mic/kg/min.

Norepinephrine was infused through central venous catheters. To avoid delay administration in the absence of central venous access it was started peripherally till center line insertion.

The predicted body weight formula

PBW = 50 + 0.91 X (centimeters of height - 152.4) for males

PBW = 45.5 + 0.91 X (centimeters of height - 152.4) for females

The Surviving Sepsis Campaign: International Guidelines for Treatment of Severe Sepsis and Septic Shock 2021 [10] was followed for the treatment of septic shock in all patients who had signed up [10]. This treatment plan started with rapid assessment of history, clinical examination and detection of sources of infection and immediate treatment was started that can mimic sepsis.

Continuous ECG, non-invasive blood pressure, and pulse oximeter monitoring of heart rate and rhythm in addition to peripheral oxygen saturation (SPO2) were carried out. Invasive blood pressure was recorded after an arterial line was implanted.

The fluid responsiveness following initial resuscitation was evaluated by pulse pressure variation (PPV) using passive leg raising test, IVC distensibility /collapsibility index

Venous blood from the legs is directed towards the intrathoracic compartment by passive leg raising. The patient could well be moved from a supine posture to a semi-recumbent position, with the trunk lowered and the patient's legs raised to a 45° angle. If the value of PPV >15%, it is suggested that the patient is responsive to fluid loading. Pulse pressure variation is a percentage and equal to the difference between the maximal PP (PPMAX) and the minimal pulse pressure (PPMIN) divided by the average of these two values (PP max – PP min) / [(PP max + PP min) / [2].

IVC assessment: when patient on supine position, obtain a subxiphoid view of the heart and identify the IVC as it enters the right atrium by ultrasound. According to type of patient spontaneously breathing or mechanically ventilated, IVC collapsibility was used for assessment in spontaneously breathing patients {IVC collapsibility = (max diameter – min diameter) / (max diameter) x 100} > 12%. In mechanically ventilated patients, IVC distensibility is a tool for fluid responsiveness if the IVC distensibility {IVC distensibility = (max diameter – min diameter) / (min diameter) x 100} > 18%.

Organ perfusion was assessed by serum lactate and capillary refill time. The capillary refill time was performed by pressure application to the nail bed till the bed blanches (10 seconds), then release and measure the time taken for colour to return. Hypoperfusion is thought to exist if the measurement time is more than 2 seconds. The severity of sepsis may be indicated by serum lactate levels that are equivalent to or higher than the upper limit of normal in the laboratory. The greater lactate clearance was correlated with favorable outcomes.

Outcome Assessment

The primary outcome measure was time required to achieve target mean arterial pressure ≥ 65 mmHg.

The secondary outcome measures were norepinephrine dose, norepinephrine duration, total amounts of IV fluids' infusion during the first 24 hours, serum lactate level, 30 days mortality rate and length of ICU stay.

Statistical Analysis

Data were gathered and tallied. The statistical analysis was performed using the Statistical Program for the Social Sciences (SPSS) version 24 (SPSS Inc. IBM SPSS statistics for windows, version 24.0, Armonk, NY: IBM Corp.).

Randomization manner was created using a computer generated, random-number list. The group assignment numbers were kept in a sealed envelope and maintained by

the study supervisor. After signing written consent, the opaque envelope was opened to determine patient's allocation

Univariate analysis, which uses number (N) and percentage (%) for qualitative data and mean (X) and standard deviation (SD) for quantitative data, was done. Several tests were used to do the bivariate analysis. The statistical differences between the quantitative variables of two groups of normally distributed data are determined using the Student's -test. The statistical differences between the qualitative variables were discovered using the Chi-square test (X2). Statistics are deemed significant with P values under 0.05.

Results

In this study, 75 patients were assessed for eligibility, 11 patients did not fulfill the inclusion criteria. The remaining 64 patients were randomly allocated into two groups (34patients in group A and 30 patients in group B). All patients were followed-up and analyzed statistically as presented at Figure 1.

Age, gender, predicted body weight, sepsis sources, and SOFA score did not differ statistically significantly between the two study groups. Table 1.

Time required to reach MAP ≥ 65 mmhg ranged from 4-10 hours and 1 hour with mean values (±SD) (7.59±1.56) and 1.00±0.00 in group A and B respectively. So, there was statistically significant decrease in the time (hours) to reach MAP ≥ 65 mmHg in group B compared with group A (P value=0.001). Figure 2

At 2 hours, 6 hours, 12 hours, and 24 hours, there was a statistically significant increase in the mean arterial blood pressure in group B compared to group A (P value < 0.05). Despite the fact that there were no statistically significant differences within the first 30 minutes and at admission (P value 0.962, 0.544 respectively). Figure 3

There was statistically significant decrease in the mean values of HR in group B compared with group A at 30 min, 2h, 6h, 12h and 24h with P value 0.024, 0.001, 0,004, 0.019 and 0.028 respectively. Figure 4

In 1h, 6h, 12h, and 24h, there was a statistically significant increase in group B's urine output compared to group A (P value < 0.05). Table 2

There was significant decrease of serum lactate level after 12h, 24h and 2nd day, total leukocyte count, serum creatinine level and blood urea level after 24h, volume of intravenous fluid, and quantity and dose of norepinephrine during 1st day, duration of norepinephrine infusion and 30 days mortality in group B compared to group A (P value < 0.05). But there was no significant difference at admission for comparison of length of ICU stay. Table 2 & 3

During admission, there was no statistically significant difference between the two study groups for blood urea, serum creatinine, serum lactate, or total leukocyte count (P value > 0.05). Table 2 & 3

There was no statistically significant difference between the two study groups' admission and 24-hour haemoglobin levels and platelet counts. Table 3.

Table 1: Demographic data of the studied groups (Age, gender, Predicted body weight and source of sepsis)

		Group A (N=34)	Group B (N=30)	p. value
Age (years)		47.18±10.14	44.30±12.44	0.312
Gender (M/F)	Male (n.,%)	15 (44.1%)	16 (53.3%)	0.462
	Female (n.,%)	19 (55.9%)	14 (46.7%)	
Predicted Body weight (Kg)		80.88±14.85	80.50±12.62	0.913
Sources of sepsis				
Pneumonia		6 (17.6%)	6 (20%)	0.910
Urinary tract infection		6 (17.6%)	7 (23.3%)	
Neck abscess,		3 (8.8%)	3 (10%)	
Skin and soft tissue infection		9 (26.5%)	9 (30%)	
Intra-abdominal infection		9 (26.5%)	4 (13.3%)	
Brain abscess		1 (2.9%)	1 (3.3%)	
SOFA Score		9.41±3.07	9.63±2.94	0.770

Data are tabulated as Mean ± S.D

Table 2: Renal functions and urine output (U.O.P) measurements of the studied groups

			Mean ± S. D	P value
Serum urea level (mmol /l)	at admission	Group A	66.26±23.78	0.1
		Group B	58.13±12.84	
	after 24h	Group A	63.15±20.64	0.001*
		Group B	43.53±10.64	
Serum creatinine level (mg/dl)	at admission	Group A	2.06±0.51	0.188
		Group B	1.90±0.41	
	after 24h	Group A	2.26±0.91	0.001*
		Group B	1.08±0.20	
U.O.P (ml) 1h.	Group A	49.12±12.88		0.001*
	Group B	61.70±8.46		
U.O.P (ml) 6h.	Group A	369.71±160.75		0.001*
	Group B	539.33±91.91		
U.O.P (ml) 12h.	Group A	733.82±251.28		0.001*
	Group B	1164±232.49		
U.O.P (ml) 24h.	Group A	1847±358.66		0.045*
	Group B	2125±270.93		

Data are tabulated as (Mean ± S.D)

P value of < 0.05 considered statistically significant

Table 3: Laboratory parameters, volume of IV fluid, quantity, dose, and duration of norepinephrine, and 30-day mortality, length of ICU stay:

		Group A (n=34)	Group B (n=30)	P value
hemoglobin (gm/dl) (Mean ± S.D)	At admission	10.38±1.07	10.80±0.84	0.091
	After 24h.	10.41±1.05	10.87±0.79	0.057
Platelet count($\times 10^9$/L) (Mean ± S.D)	At admission	239.38±55.57	246.67±67.52	0.638
	After 24h	238.26±54.36	245.30±67.65	0.646
Total leukocyte count (cells× 10^9/L) (Mean ± S.D)	At admission	23.71±4.43	21.53±4.45	0.055
	After 24h	20.12±4.24	15.93±3.75	0.001*
Serum lactate (mmol/ L) (Mean ± S.D)	At admission	3.09±0.43	3.01±0.47	0.475
	After12 hours	3.08±0.50	2.67±0.29	0.001*
	After 24 hours	2.59±0.46	2.08±0.26	0.001*
	After 2nd day	2.00±.045	1.18±0.27	0.001*
Length of ICU stay (days) (Mean ± S.D)		20.53±8.14	19.93±8.10	0.770
Volume (L) of intravenous fluid during 1st day (Mean ± S.D)		3.62±0.83	2.27±0.22	0.001*
Quantity of norepinephrine (mg)during 1st day (Mean ± S.D)		31.87±17.45	17.80±7.95	0.001*
Dose of norepinephrine (mic/kg/min) during 1st day		0.27±0.13	0.15±0.0 6	0.001*
Duration of norepinephrine (Days) (Mean ± S.D)		5.71±2.04	3.90±1.12	0.001*
30-day mortality	Live (no.,%)	25 (73.5%)	26 (86.7%)	0.01*
	Die (no.,%)	9 (26.5%)	4 (13.3%)	

P value of < 0.05 considered statistically significant

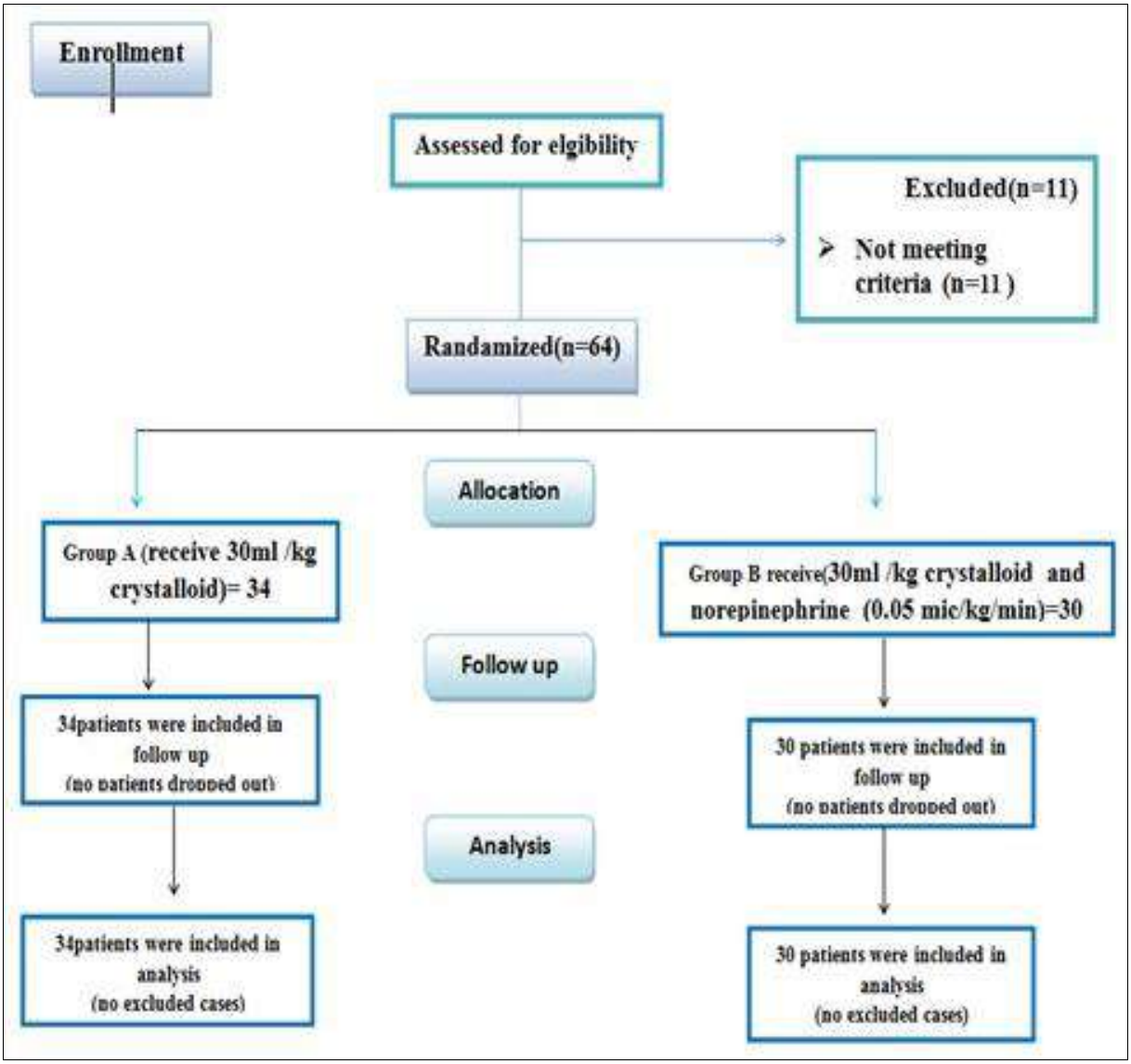

Fig 1: Consort flowchart of the study groups

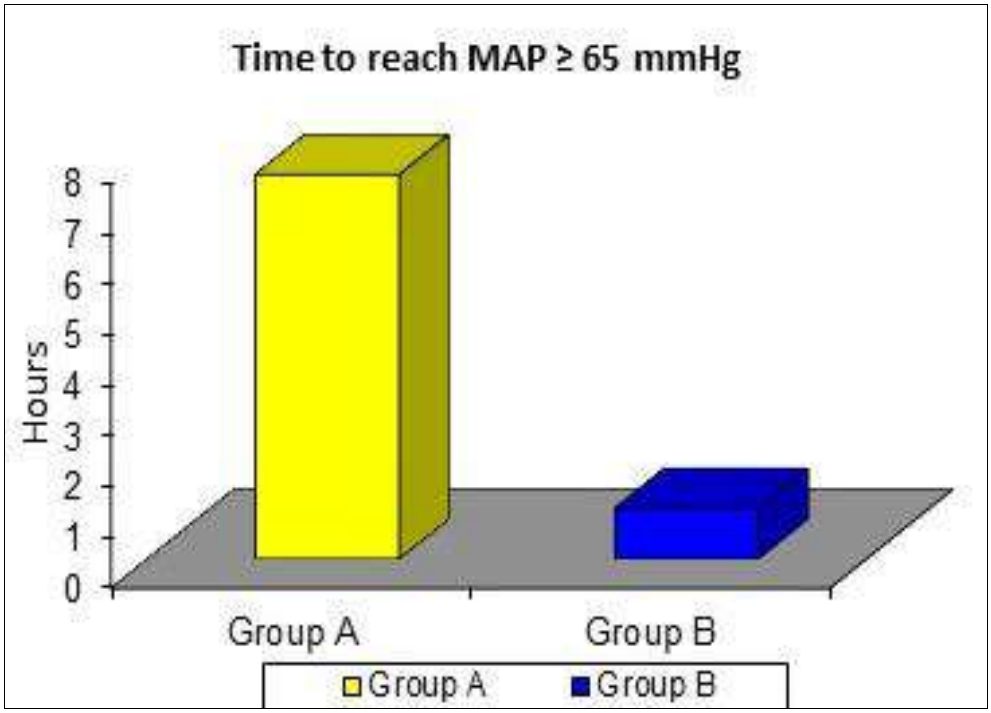

Fig 2: Time required to reach ≥ 65 mmHg of both the studied groups

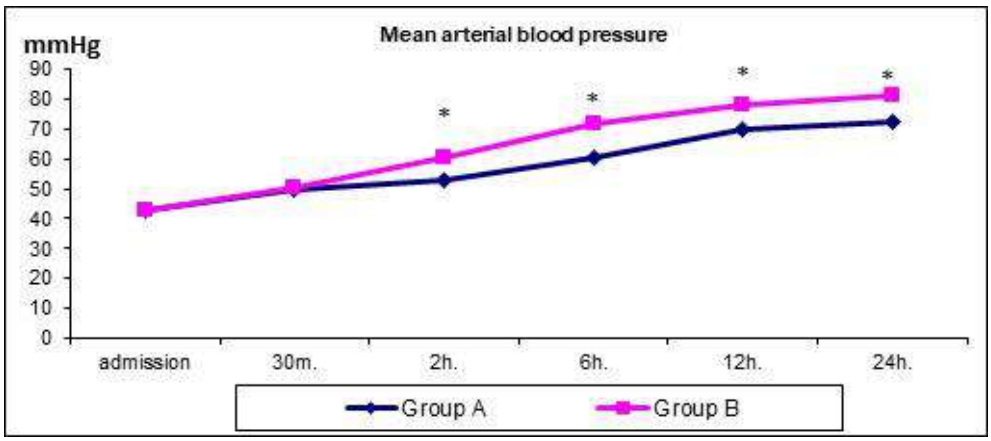

Fig 3: Mean arterial blood pressure of both the studied groups

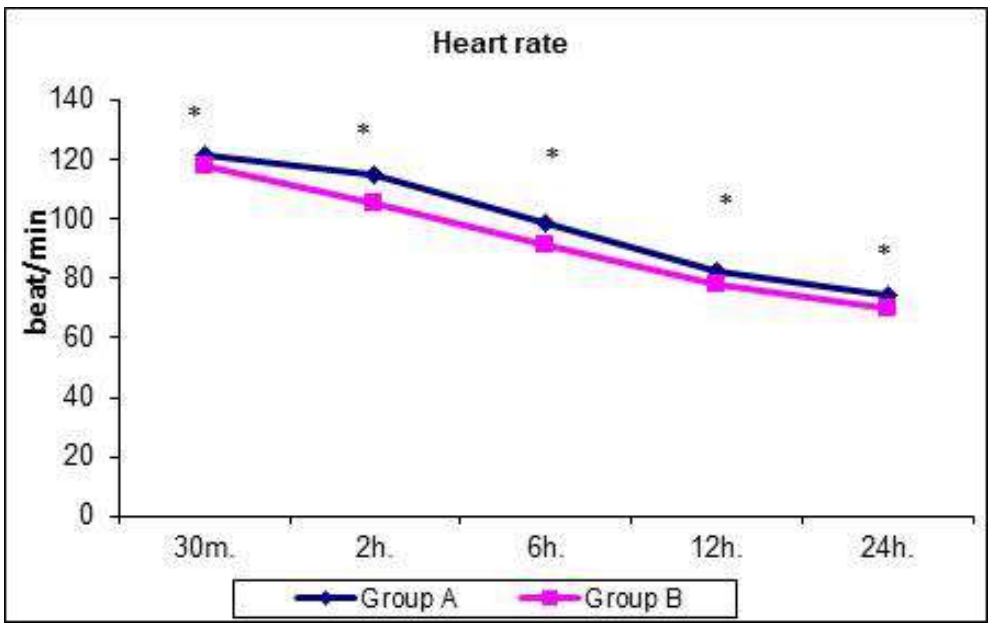

Fig 4: Heart rate of both the studied groups.

Discussion

Septic shock has a complex pathophysiology that affects multiple organs. Vasodilatation, relative and absolute hypovolemia, cardiac dysfunction, increased metabolic demand, and microcirculation dysfunction are all parts of this intricate process. Sepsis-induced hypotension is caused by a concomitant reduction in vascular tone and hypovolemia [10].

Extra vascular edema, lung dysfunction, and tissue oxygenation may all be negatively impacted by large fluid resuscitation. Therefore, it is recommended to start vasopressors within six hours specially after failure of initial fluid resuscitation to restore MAP ≥ 65 mmhg. Norepinephrine is considered as the first-choice vasopressor due to its agonist action on alpha1- and beta1 receptors. The net results are increase in vascular tone and improved myocardiac contractility [11].

The early initiation of norepinephrine avoids prolonged severe hypotension, increases stressed blood volume which improve preload, so this improves cardiac output. It also improves MAP in severely hypotensive patients which leads to improvement of microvascular blood flow in pressure-dependent vascular beds and avoids fluid overload [4].

In accordance with our results: Morimatsu *et al*., [12], who concluded that prompt and exclusive NE infusion was linked with a high survival rate, decrease of the plasma lactate level after 24 hours of resuscitation and that it quickly recovered a sufficient MAP in all patients as all patients reached their goal mean arterial pressure (MAP) within 30 minutes of starting resuscitation.

Our results reinforce those of Bai *et al*., [13], who discovered that morality incidence rose with every 1-hour delay in the beginning of norepinephrine treatment within the first six hours following the presentation of septic shock. Regarding mean arterial pressures, serum lactate, the length of hypotension and norepinephrine treatment, and the amount of norepinephrine administered in a 24-hour period, Bai *et al*., findings were similar to our findings.

Also, in accordance with our results Hamzaoui *et al*., [14], who concluded that norepinephrine administration during early resuscitation in patients with septic shock improved cardiac output and organ perfusion, improved target MAP values greater than 65 mm Hg. This resulted in decreased blood lactate.

Our findings are in line with those made by Li *et al*., [15], who revealed that norepinephrine infusions started early in septic shock patients reduced short-term mortality, shortened time to target MAP, and decreased risk of fluid overload.

Our research is consistent with that of Hamzaoui [16] who concluded that an early combination of vasopressors and fluids provide effective therapeutic plan for septic shock due to different causes. This combination increased the mean systemic pressure more than fluid alone with correction of hypotension. It reduced risk of fluid overload with reduction of hemodilution produced by fluid overload. It increased oxygen delivery improving outcomes finally.

Our research is consistent with that of Xu *et al*., [17], who showed the same results of this study regarding the total amounts of fluid therapy, 28-day mortality, duration of noradrenaline infusion and time required to achieve target MAP. While in contrast with our result: they found that duration of intensive care unit and hospital stays were shorter in the early norepinephrine initiation group. Early norepinephrine initiation may delay or partially reverse rapid onset organ failure.

Also, in association with our results**,** Permpikul *et al*., [18], who evaluated that Compared to control treatment, early low-dose norepinephrine administration in sepsis led to early hypotension management by 6 hours. They discovered that the early norepinephrine infusion facilitated faster establishment of the target MBP (65 mm Hg), increased urine output (0.5 ml/kg), and improved lactate clearance. In contrast to our findings, they found no change in the 28-day mortality rate or the total volume of fluid administered between the early and late NE infusion groups. After the sixth hour, there were no statistically significant variations in the norepinephrine dosage across the groups. There were different causes explaining their adverse results. Their study did not provide the resuscitation fluid control rate which leads to differences of the patients' data. Permpikul *et al* study was a single-center trial, needing more studies to ensure their results.

On other hand, Subramanian *et al*., study [19] results were against our results. They discovered that without alterations in lactate levels and urine output, liberal use of vasopressors had no effect on hospital mortality. Their study's retrospective observational design and single-center execution helped to explain this. The critically ill patients who were included in the study had varying responses to their critical illness scores, and they used generous amounts of vasopressors in conjunction with mechanical ventilation and fluid resuscitation. They were able to determine that the progression of organ failures in septic shock was slowed down by early administration of appropriate antibiotics and optimization of organ perfusion, but not by extensive use of vasopressors.

Furthermore, there are certain drawbacks to our study, such as the relatively limited number of patients, which may necessitate further research with a larger sample size. The results of our study need to be confirmed by more randomised studies. The effects of early norepinephrine infusion on the effectiveness of corticosteroid therapy and antibacterial therapy require further research.

Conclusion

Norepinephrine, when administered as part of initial resuscitation of sepsis induced hypotension result in decreased time to reach target MAP, decrease IV fluid requirement, lowers blood lactate levels, and decreases mortality rate. Norepinephrine is a promising early resuscitation agent for septic shock, and further study of its early administration is warranted.

Availability of the data and material

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

Consent for publication: No individual data is presented in the study

Financial support and sponsorship: Nil

Declaration of Interest: Nil

References

1. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW,

Liu VX, Deutschman CS, *et al*. Sepsis Definitions Task Force. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):775-87.
2. Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Crit Care. 2019 May 31;23(1):196.
3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*., The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10.
4. Hamzaoui O, Shi R. Early norepinephrine use in septic shock. J Thorac Dis. 2020 Feb;12(Suppl 1):S72-S77.
5. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*., Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304-377.
6. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018 Jun;44(6):925-928.
7. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence. 2014 Jan 1;5(1):73-9.
8. Kelm DJ, Perrin JT, Cartin-Ceba R, Gajic O, Schenck L, Kennedy CC. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock. 2015 Jan;43(1):68-73.
9. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002 Jun;121(6):2000-8.
10. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247.
11. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med. 2002 Jul 1;166(1):98-104.
12. Morimatsu H, Singh K, Uchino S, Bellomo R, Hart G. Early and exclusive use of norepinephrine in septic shock. Resuscitation. 2004 Aug;62(2):249-54.
13. Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, *et al*. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 2014 Oct 3;18(5):532.
14. Hamzaoui O, Jozwiak M, Geffriaud T, Sztrymf B, Prat D, Jacobs F, *et al*. Norepinephrine exerts an inotropic effect during the early phase of human septic shock. Br J Anaesth. 2018 Mar;120(3):517-524.
15. Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. Crit Care. 2020 Aug 6;24(1):488.
16. Hamzaoui O. Combining fluids and vasopressors: A magic potion? J Intensive Med. 2021 Nov 14;2(1):3-7.
17. Xu F, Zhong R, Shi S, Zeng Y, Tang Z. Early initiation of norepinephrine in patients with septic shock: A propensity score-based analysis. Am J Emerg Med. 2022 Apr;54:287-296.
18. Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial. Am J Respir Crit Care Med. 2019 May 1;199(9):1097-1105.
19. Subramanian S, Yilmaz M, Rehman A, Hubmayr RD, Afessa B, Gajic O. Liberal vs. conservative vasopressor use to maintain mean arterial blood pressure during resuscitation of septic shock: an observational study. Intensive Care Med. 2008 Jan;34(1):157-62.

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