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ORIGINAL RESEARCH **RESUSCITATION/LIFE SUPPORT**

The effect of using low dose norepinephrine before hypotensive resuscitation in hemorrhagic shock; a randomized controlled trial

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ABSTRACT

Background & Objectives: Hemorrhagic shock is not a very rare occurrence in big hospitals. It might be encountered in the emergency room (ER) or in the operating rooms (OR). A rapid response and systematic management will save the life of the victim. The objective of this research was to investigate the impact of a low dose of norepinephrine (NE) administered prior to the initiation of hypotensive resuscitation in patients with hemorrhagic shock.

Methodology: This randomized controlled trial was conducted on 200 participants, at least 18 years old, classified as severely traumatized and had significant hemorrhage with mean arterial pressure ranging from 65 to 75 mmHg. We divided the patients into two equal groups. Group I received a low dose of NE (< 0.3 µg/kg/min) concurrently with resuscitation fluids. Group II received resuscitative fluids only. If the resuscitative fluids failed to keep mean arterial pressure (MAP) > 65 mmHg, the patient was progressively administered NE even with high doses (0.05 to more than 0.3 µg/kg/min). The primary outcome was 24-hour mortality. In-hospital mortality, incidence of acute kidney injury (AKI), and duration of hospital and intensive care unit (ICU) stay constituted the secondary outcomes.

Results: Group I had lower 24-hour mortality compared to Group II (3% vs 13%; $P < 0.05$). Compared to Group II, Group I needed reduced amount of fluid resuscitation within 24 h, had lower serum lactate levels at 6 and 12 h, and lower serum creatinine at 6, 12, and 18 h ($P < 0.001$). Group I had a lower incidence of mechanical ventilation (13% vs 27%), hospital and ICU stays, and in-hospital mortality (9% vs 21%) ($P < 0.05$). There was a lack of disparity seen in the incidence of AKI and duration of mechanical ventilation.

Conclusion: Low-dose norepinephrine infusion during the early period of hypotensive resuscitation reduces resuscitative fluid requirement, improves tissue perfusion, preserves renal function, and lowers mortality in hemorrhagic shock patients.

Abbreviations: AKI - acute kidney injury; APACHE III - Acute Physiology And Chronic Health Evaluation III; HS - hemorrhagic shock; ICU - intensive care unit; MAP - mean arterial pressure; NE - Norepinephrine

Keywords: Hemorrhagic Shock; Hypotensive Resuscitation; Norepinephrine; Fluid Therapy; Renal Protection; Mortality; Low Dose

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1. INTRODUCTION

Severe trauma constitutes a worldwide public health co ncern representing a mortality rate exceeding 10%.[1] Trauma patients experiencing hemorrhagic shock (HS) face a substantially increased risk of death.[2]

Current therapeutic guidelines recommend a multifaceted approach, including fluid resuscitation, blood and blood products transfusion, use of vasopressors and definitive physical hemorrhage control.[3] Researchers have been exploring alternative fluid resuscitation strategies, as well as delayed, hypotensive, and hypothermic approaches, for the management of uncontrolled shock. These novel techniques have shown promise in improving both clinical outcomes as well as laboratory parameters of the patients.[4]

Permissive hypotensive resuscitation has been found in a number of trials to be more effective than normotensive resuscitation in reducing blood loss and, consequently, the mortality rate in shock patients.[5,6] Norepinephrine (NE) possesses a powerful stimulation effect on α-adrenergic receptors in the body. It has the ability to excite α_1 adrenergic receptors in the smooth muscles of the vascular system in the extremities.[7] When administered in significant quantities, NE has the potential to cause excessive vasoconstriction of the arterioles; subsequently, this might result in disruption of the circulation and thus hypoxia of the tissues. It has been advised to administer NE in a dose ranging from 0.05 to 0.3 g/kg/min, based on the prerequisite of appropriate volume resuscitation.[8,9]

At this time, there is not much of the comprehensive data concerning the efficacy of NE being administered to patients who have HS. Emerging preclinical studies suggest the potential benefits of low-dose NE administration for animals during HS resuscitation.[10] Early administration of vasopressors may have deleterious circulatory effects in comparison to the use of fluids for resuscitation alone, as demonstrated by a prior study.[11]

The administration of vasopressors in the early stage of HS, on the other hand, continues to be a debatable topic.[12] The primary factor to consider is the fact that vasopressors have the potential for severe vasoconstriction, which has the potential to exacerbate tissue ischemia.[13] The objective of this research was to investigate the impact of a low dose of NE given prior to the initiation of hypotensive resuscitation.

2. METHODOLOGY

This open-label, randomized research was conducted on 200 participants of both sexes, at least 18 y old, classified as severely traumatized, had significant hemorrhage with mean arterial pressure (MAP) ranged from 65 to 75 mmHg. Following approval from the Ethical Committee of Tanta University Hospitals (approval code: 36264PR430/11/23), the research was conducted between December 2023 and April 2024. Written informed consent was obtained from the patient or their legal guardians.

The exclusion criteria were; cardiac arrest, catastrophic brain or spinal injury (due to varying target blood pressures), mortality within six hours of admission, and pregnancy.

2.1. Randomization and blindness

The cases were randomized using a computer-generated sequence by sealed opaque envelopes in a parallel manner. The patients were categorized into two equal groups: Group I received resuscitative fluid and a low dose of NE (0.05-0.2 μg/kg/min) concurrently with resuscitative fluid [administered at the onset of the patient's arrival in the emergency department to keep MAP > 70 mmHg]. Group II received resuscitative fluids only. If the resuscitative fluids failed to keep MAP > 65 mmHg, the patient was progressively administered NE even with high doses (0.05 μg/kg/min to more than 0.3 μg/kg/min). The study was open label due to differences in the techniques.

The following parameters were recorded for every patient; age, sex, body mass index (BMI), medical history, including hypertension, myocardial infarction, congestive heart failure, chronic pulmonary disease, diabetes mellitus, and kidney disease). Prehospital status including heart rate, fluid quantity infused, whether intubatedor not, were also recorded. On admission status (MAP, HR), intubation, blood lactate, and serum creatinine), Acute Physiology And Chronic Health Evaluation III (APACHE III) score on the first day, and NE use were noted as baseline characteristics within 24 h of admission.

The primary outcome was 24-hour mortality. In-hospital mortality, incidence of acute kidney injury (AKI), and duration of hospital and ICU stay constituted the secondary outcomes.

2.2. Sample size calculation

The G power 3.1.9.2 (Universitat Kiel, Germany) was utilized to compute the sample size. The sample size was determined using the 24-hour mortality rate from a pilot study on ten patients as 10% in Group I and 30% in Group II. Based on 90% power and a 0.05 error, the

Table 1: Patient characteristics and medical history of the studied groups

Parameters		Group I (n = 100)	Group II (n = 100)	P value
Age (y)		50.27 ± 14.94	49.34 ± 14.6	0.657
Gender	Male	65 (65)	59 (59)	0.382
	Female	35 (35)	41 (41)	
Weight (kg)		79.29 ± 13.31	77.48 ± 10.95	0.295
Height (cm)		168.65 ± 8.09	169.33 ± 6.59	0.515
BMI (kg/m^2)		28.05 ± 5.33	27.11 ± 4.19	0.167
APACHE III		70.4 ± 5	71.64 ± 5.65	0.102
Medical history	Hypertension	28 (28)	31 (31)	0.642
	Diabetes mellitus	25 (25)	23 (23)	0.741
	Myocardial infarction	22 (22)	26 (26)	0.508
	Congestive heart failure	10 (10)	14 (14)	0.384
	Chronic pulmonary disease	13 (13)	11 (11)	0.663
	Chronic Kidney disease	16 (16)	21 (21)	0.363

Data presented as mean ± SD or frequency (%). APACHE: Acute physiology and chronic health evaluation.

allocation ratio was 1:1 and eighteen cases were added to each group to cater for the drop-outs; one hundred patients were assigned to each cohort.

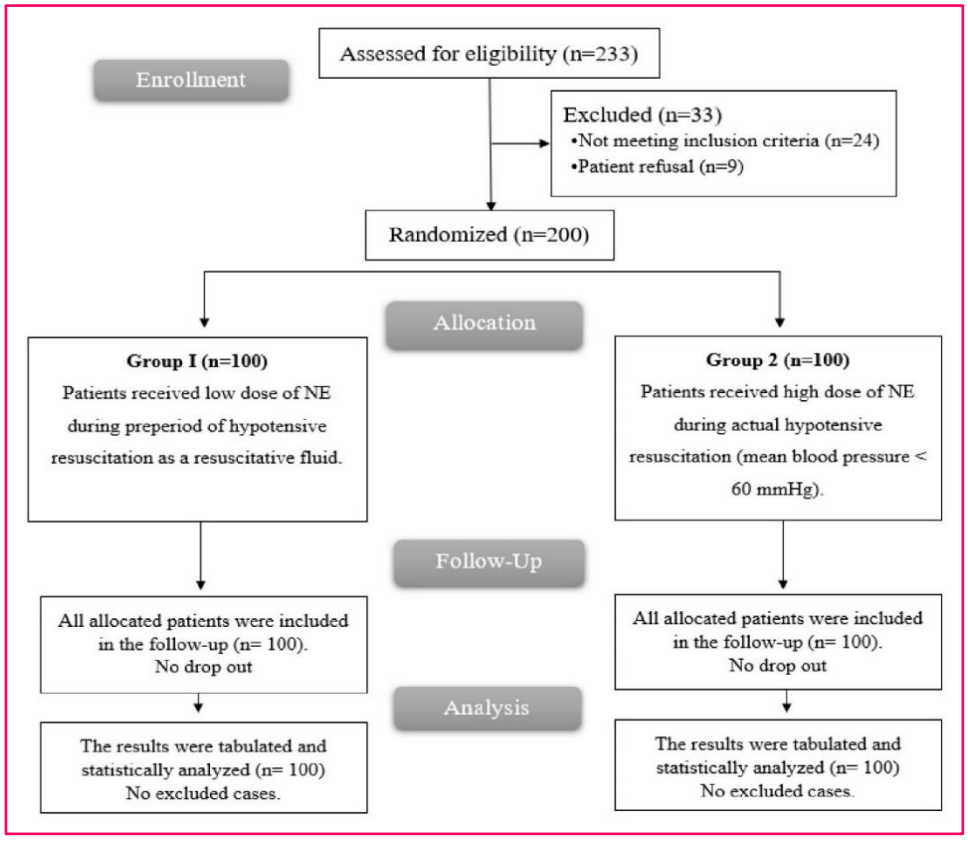

Figure 1: CONSORT flowchart of the enrolled participants.

2.3. Statistical analysis

SPSS v27 was utilized for the statistical analysis (IBM©, Armonk, NY, USA). Histograms and the Shapiro-Wilks test were utilized to assess the normality of the data distribution. Mean and standard deviation (SD) were utilized to present quantitative parametric data, which were subsequently analyzed using the unpaired Student's t-test. Quantitative non-parametric data were analyzed using the Mann Whitney test and were presented as the median and interquartile range (IQR). The frequency and percentage values of qualitative variables were used for analysis, with the appropriate tests being the Chi-square test or Fisher's exact test. $P < 0.05$ was deemed to be statistically significant.

Table 2: Resuscitation data of the studied groups

	Group I (n = 100)	Group II (n = 100)	P value
Total fluid resuscitation within 24 h (L/24 h)	4.39 ± 1.15	6.03 ± 1.43	**< 0.001***
Packed RBCs (units)	4.21 ± 0.83	4.4 ± 0.99	0.145
Plasma (units)	1.89 ± 0.84	2.08 ± 0.71	0.085
Platelets (units)	0.96 ± 0.83	1.17 ± 0.91	0.090

*Data are presented as mean ± SD or median (IQR). *P ≤ 0.05 considered as significant*

Table 3: Norepinephrine dose of the studied groups

Variable	Group I (n = 100)	Group II (n = 100)	P value
Total dose of norepinephrine within 24 h (µg/kg)	4386.46 (1451.08–6180.92)	1512000 (0–5346000)	**< 0.001***
Duration norepinephrine used (min)	996 ± 641.02	236.55 ± 454.63	**< 0.001***

*Data are presented as mean ± SD or median (IQR). **P ≤ 0.05 considered as significant*

Table 4: Serum lactate and creatinine of the studied groups

Parameter	Group I (n = 100)	Group II (n = 100)	P value
Serum lactate (mmol/L)			
Baseline	2.28 ± 0.51	2.31 ± 0.38	0.617
6 h	2.64 ± 0.58	3.09 ± 0.43	**< 0.001***
12 h	3.25 ± 0.64	4.04 ± 0.51	**< 0.001***
18 h	2.98 ± 0.54	3.09 ± 0.47	0.130
24 h	2.55 ± 0.53	2.62 ± 0.43	0.370
Serum creatinine (mg/dl)			
Baseline	1.11 ± 0.27	1.05 ± 0.18	0.078
6 h	1.26 ± 0.28	1.41 ± 0.2	**< 0.001***
12 h	1.56 ± 0.31	1.89 ± 0.31	**< 0.001***
18 h	1.34 ± 0.32	1.61 ± 0.3	**< 0.001***
24 h	1.27 ± 0.32	1.34 ± 0.28	0.107

*Data presented as mean ± SD. *P ≤ 0.05 considered as significant.*

3. RESULTS

Eligibility was determined for 233 patients with 200 of them participating in this investigation; 24 patients failed to meet the requirements, and 9 patients refused to participate. The patients had been assigned at random to each of the two equal groups. All allocated patients were followed up in statistical analysis (Figure 1).

There were no significant differences seen in demographic data and medical history between the two groups (Table 1).

Fluid resuscitation within 24 h was significantly lower in Group I than in Group II (P < 0.001). The number of packed RBCs, plasma and platelet units were insignificantly different between both groups (Table 2).

MAP and HR were significantly higher at 30, 45, 60 and 90 min in Group I than in Group II (P < 0.05) and was insignificantly different at baseline, at 15, 75, and 105 min, as well as at 2, 4, 8, 12, 18 and 24 h (Figure 2).

Total dose of NE within 24 h was significantly lower in Group I than in Group II (P < 0.001). Duration of NE was significantly higher in Group I than Group II (P < 0.001) (Table 3).

Serum lactate was insignificantly different at baseline, at 18 and 24 h between both groups and was significantly lower at 6 h and 12 h in Group I than in Group II (P < 0.001). Serum creatinine was insignificantly different at baseline and 24 h between both groups and was

Table 5: Mechanical ventilation, ICU and hospital stay, AKI and mortality

Parameter	Group I (n = 100)	Group II (n = 100)	P value
Need for mechanical ventilation	13 (13)	27 (27)	**0.013***
Duration of mechanical ventilation (days)	4.85 ± 3.6	5.41 ± 5.88	0.754
ICU stay (days)	7.04 ± 2.88	9.73 ± 5.67	**< 0.001***
Hospital stay (days)	15.11 ± 6.45	17.58 ± 9.29	**0.03***
AKI	17 (17)	28 (28)	0.063
24-h mortality	3 (3)	13 (13)	**0.016***
In hospital mortality	9 (9)	21 (21)	**0.017***

*Data presented as mean ± SD or frequency (%). *P ≤ 0.05 considered as significant.*

significantly lower at 6, 12 and 18 h in Group I than in Group II (P < 0.001) (Table 4).

24-h mortality, need for mechanical ventilation, ICU stay, and in-hospital mortality were significantly lower in Group I than Group II (P < 0.05). Days of mechanical ventilation and AKI were insignificantly different between both groups (Table 5).

4. DISCUSSION

Current research investigated the effects of two different dosing strategies of NE during the preperiod of hypotensive resuscitation in patients with HS. Fluid resuscitation within the first 24 h was significantly lower in Group I compared to Group II (P < 0.001). This finding suggests that the continuous low-dose norepinephrine strategy employed in Group I may have facilitated better preservation of intravascular volume and reduced the need for aggressive fluid resuscitation.

Our results are in line with a recent investigation by Zhang et al. who demonstrated reduced fluid resuscitation requirements with early norepinephrine administration compared to delayed norepinephrine (5150 vs. 6672 ml) in patients with HS, leading to improved hemodynamic stability.[14] However, it is noteworthy that the total fluid volume used in their study remained higher compared to our investigation. Excessive fluid administration is associated with various problems including, pulmonary edema, and abdominal compartment syndrome.[15-17] Therefore, the lower fluid requirement observed in Group I could potentially improve clinical outcomes and decrease complications related to fluid overload.

Interestingly, the number of packed RBCs, plasma, and platelet units transfused was not significantly different between the two groups. This observation implies that the continuous low-dose norepinephrine strategy did not compromise the need for blood product transfusions,

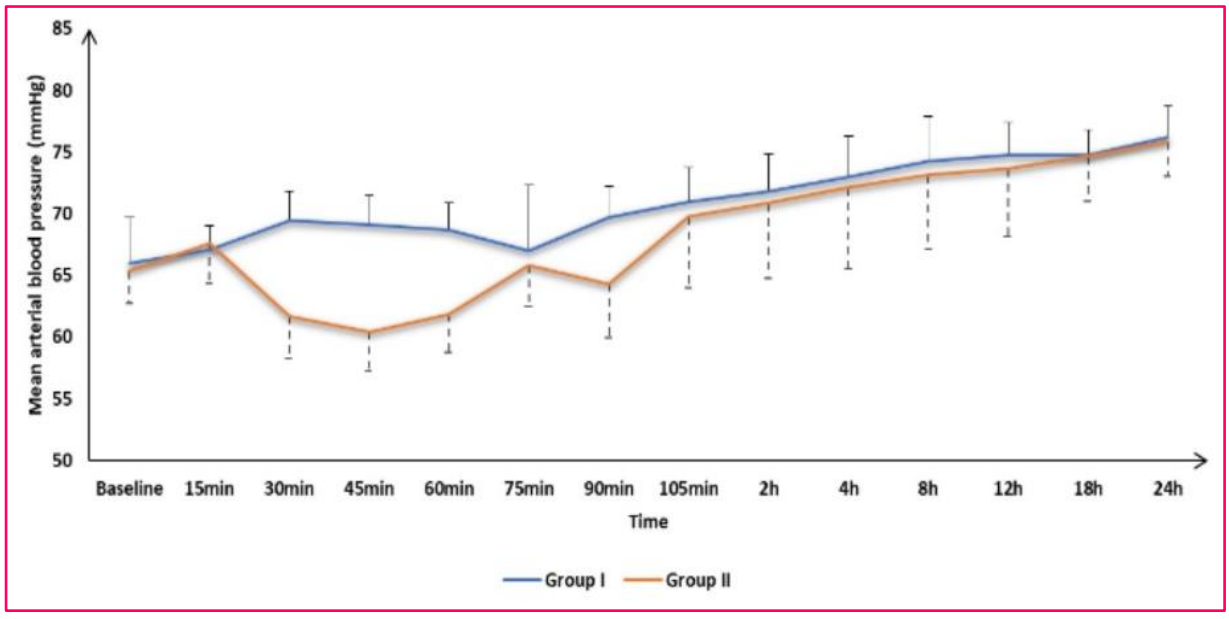

Figure 2: Comparative mean arterial blood pressure in the groups

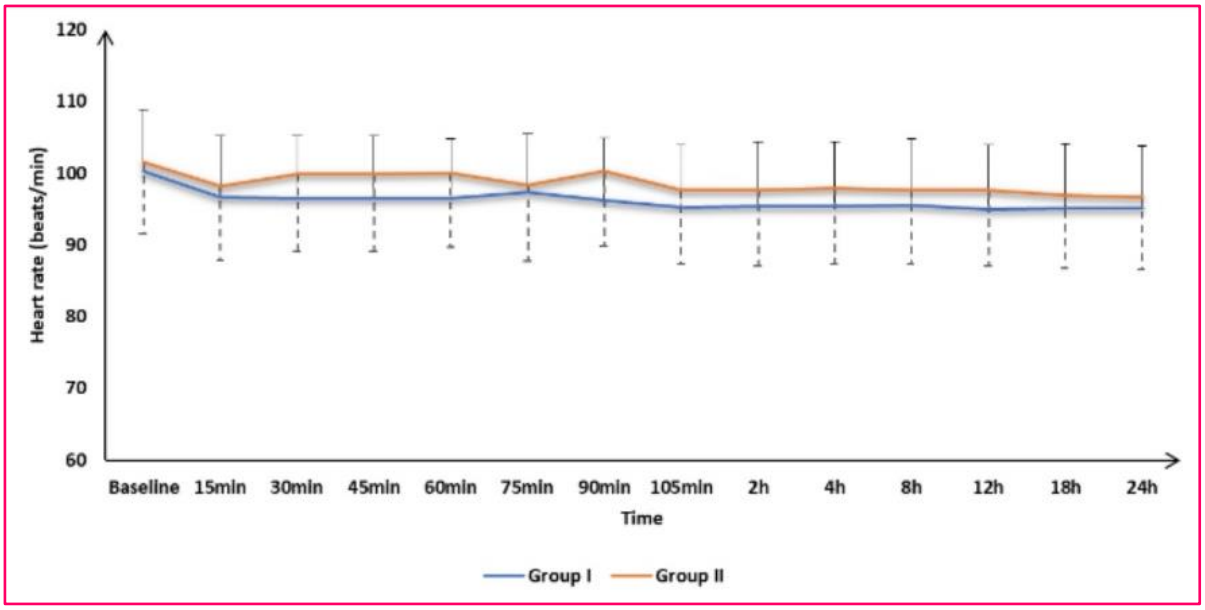

Figure 3: Comparative heart rates in the studied groups

which are crucial in managing HS and restoring oxygen-carrying capacity.[18]

While the European guideline (2019) recommend use of NE for maintaining target blood pressure, the timing remains unclear.[6] The autonomic nervous system relies on NE to perform crucial functions in the regulation of blood pressure and homeostasis.[19] The significantly higher MAP and HR observed in Group I at specific time points (30, 45, 60, and 90 min) compared to Group II may be attributed to the continuous infusion of norepinephrine, which could have provided better hemodynamic support during the initial resuscitation phase. In contrast, Zhang et al. reported lower MAP during early NE administration compared to delayed administration, while Zhou et al. demonstrated that low-dose NE (0.1-0.5 μg/kg/min) prolonged the golden treatment time for HS in rats.[10,14]

The total dose of NE administered within 24 h was significantly lower in Group I compared to Group II ($P < 0.001$). Additionally, the duration of NE administration was significantly prolonged in Group I than Group II ($P < 0.001$). These findings highlight the contrasting dosing strategies employed in the two groups and suggest that the early use of low-dose NE in Group I was more efficient.

Lactate levels serve as an indirect marker of tissue hypoperfusion, oxygen debt, and the severity of HS.[18, 20, 21] Significantly lower serum lactate levels observed in Group I at 6 and 12 h suggest that the continuous low-dose NE strategy facilitated improved tissue perfusion and more efficient clearance of lactate during the early resuscitation phase. This finding contrasts with Zhang et al.,[14] who reported no significant difference in lactate levels between early and delayed norepinephrine administration, but aligns with Zhou et al.,[10] who demonstrated reduced lactate levels with NE administration, particularly at 0.3 μg/kg/min. Furthermore, the significantly lower serum creatinine levels in Group I at 6, 12, and 18 h imply a potential renoprotective effect of the continuous low-dose norepinephrine strategy during the early resuscitation period. This finding is consistent with the observations of Gordon et al., who reported lower serum creatinine levels in patients with septic shock receiving NE.[22] However, Zhang et al. found no significant difference in creatinine levels between early and delayed NE administration, while Zhou et al. reported decreased creatinine levels after hypotensive resuscitation with NE, suggesting improved kidney function.

Notably, the need for mechanical ventilation, ICU stay, 24-h mortality, and in-hospital mortality were significantly lower in Group I compared to Group II. These findings suggest that the continuous low-dose NE strategy employed in Group I may have contributed to improved clinical outcomes and reduced resource utilization. However, it is important to note that the days of mechanical ventilation and the incidence of AKI were not significantly different between the two groups. These findings suggest that the continuous low-dose norepinephrine strategy may contribute to improved clinical outcomes and reduced resource utilization, in line with previous studies investigating the effects of norepinephrine during resuscitation. For instance, Gauss

et al. reported 24-hour and in-hospital mortality rates of 18% and 36%, respectively, in trauma patients receiving prehospital NE administration.[23] Similarly, Zhang et al. observed lower in-hospital mortality (30.7% vs. 45%) with early NE administration compared to delayed administration in patients with traumatic hemorrhage.

5. LIMITATIONS

The investigation was done only at a single center, perhaps limiting the extent to which the results may be generalized. Additionally, the study did not evaluate the long-term consequences or any difficulties beyond the first period of resuscitation. Furthermore, the study's sample size was rather small, potentially limiting the capacity to identify disparities in some secondary outcomes, such as the prevalence of acute kidney injury (AKI).

6. CONCLUSION

Continuous low-dose norepinephrine strategy (< 0.3 μg/kg/min) in the early phase of resuscitation of victims of hemorrhagic shock was associated with reduced fluid requirement, better preservation of renal function, improved lactate clearance, and lower mortality rates compared to the use of fluids only, which ultimately required higher total doses (> 0.3 μg/kg/min) of norepinephrine. These findings suggest that the careful use of low-dose norepinephrine during the early phase of hypotensive resuscitation in patients with hemorrhagic shock may offer clinical benefits and improved outcomes.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

We gratefully thank Faculty of Medicine, Tanta University, Tanta, Egypt for their help and guidance in conducting this study.

9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

RMM: developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript, and is a guarantor.

AGA: contributed to the development of the protocol, abstracted data.

AAE: prepared the manuscript.

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