Time to norepinephrine in sepsis – a prospective inception cohort study

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1 Introduction

Current guidelines recommend norepinephrine (NE) as the first-line vasoactive agent to maintain a mean arterial pressure (MAP) of 65 mmHg in patients with sepsis (1). While evidence for the optimal timing of NE initiation is limited, early administration, potentially via a peripheral line, is recommended (1). Two randomized controlled trials have investigated the immediate administration of NE in patients with suspected septic shock in the emergency department (2, 3), though these studies were relatively small. In Sweden, the speed of NE initiation and the departments responsible for its administration are unknown. Fluid accumulation is an independent risk factor for multi-organ dysfunction, including respiratory failure, intra-abdominal hypertension, acute kidney injury (AKI), and mortality (4-6). It remains unclear whether early norepinephrine administration can reduce fluid requirements in patients with sepsis and hypotension.

1.1 Rationale for the current study

If NE initiation is delayed and excessive fluids are administered during this period, it could necessitate a change in current Swedish clinical practice. This study aims to provide data on the time to NE initiation and fluid administration in adult patients with sepsis and hypotension in Sweden.

1.2 Research questions

1. What is the time interval between suspected sepsis with hypotension and the initiation of NE?
2. What volumes and types of fluids are administered prior to NE initiation and during the first 24 hours?
3. Is there an association between time to NE and amounts of fluids the first 24 hours?

1.3 Objectives

1. To describe the use of NE in patients with sepsis in Swedish hospitals.
2. To describe the volume and type of fluids administered during the first 24 hours in Swedish hospitals.
3. Explore the association between amounts of fluids and the timing of NE initiation.

1.4 Hypothesis

1. A longer time to NE initiation is associated with a greater volume of fluid administration during the first 24 hours of sepsis.

2 Methods

2.1 Study design and setting

We will conduct a prospective, multicenter cohort study involving emergency departments across Sweden. Patients will be enrolled over a 28-day period.

2.2 Number of subjects

We aim to include approximately 204 patients who present to the emergency department in Swedish hospitals with sepsis and hypotension and where at least 61 subsequently receive NE.

2.3 Expected duration of the study

Each participating site will select a 28-day period for patient enrollment. Follow-up will continue for 90 days post-enrollment. The study is anticipated to commence on [Start Date] and conclude on [End Date].

2.4 Participants

All patients presenting to the emergency department at each site with suspected sepsis and hypotension will be screened for eligibility by local investigators.

2.5 Eligibility

2.5.1 Inclusion criteria

1. Age ≥ 18 years
2. Suspected sepsis defined as, blood cultures obtained and intravenous antibiotics administered.
3. Hypotension defined as MAP < 65 mmHg.

2.5.2 Exclusion criteria

1. Prior enrollment in this study.

2.6 Discontinuation of data collection

Data collection will go on for 24 hours.

2.7 Study closure

The study will end after the pre-planned number of participants has been enrolled.

3 Outcome measures

3.1 Primary outcome

Time from arrival at the emergency room to initiation of NE in minutes.

3.2 Secondary outcomes

1. Amount (mL) and types of fluids used during the first 24 hours after arrival to the emergency
2. Association between the time of initiation of NE and amounts of fluids during the first 24 hours.

4 Variables for baseline data and primary and secondary outcomes

4.1 Baseline variables

1. Age (years)
2. Sex (male, female)
3. Hospital admission date and time
4. eSOFA score (number)
5. Betalactam- or aminoglycoside antibiotics (y/n)
6. Blood cultures drawn (y/n)
7. MAP < 65 mmHg (y/n)
8. Charlson comorbidity index (number)

4.2 Outcome variables

1. Time from admission to NE (minutes)
2. Sodium chloride 0,9 % administered prior to NE (mL)
3. Balanced isotonic fluids (eg Ringer's acetate or Plasmalyte) administered prior to NE (mL)
4. Albumin administered prior to NE (mL)

5 Statistical methods

5.1 Population to be analyzed

Analysis will be based on intention to treat.

5.2 Sample size calculation

We aim to recruit patients until we have 61 patients who received norepinephrine. This sample size is based on the assumption that we wish to estimate the mean time to norepinephrine with a confidence interval width of approximately 4 hours, assuming a standard deviation of 8 hours. Given an estimated norepinephrine administration rate of 30% among eligible patients, we anticipate needing to recruit approximately 204 patients. The final confidence interval width for the time to norepinephrine will depend on the observed standard deviation in the final sample of 61 patients.

5.3 Baseline characteristics

Baseline characteristics will be presented in a table with the variables listed above. Continuous variables will be presented with mean and standard deviation if they are normally distributed and as median and interquartile range if they are not normally distributed. Categorical variables will be presented as numbers (n) and corresponding percentages (%).

5.4 Primary outcome

Time to NE will be presented as minutes and confidence interval (95 %).

5.5 Secondary outcome

1. Amounts and types of fluids prior to NE will be presented as type and mL.
2. Association between time to NE and amounts of fluids during the first 24 hours. will be analyzed by linear regression and adjusted for age, the worst eSOFA-score within 6 hours from arrival at the emergency, Charlson comorbidity index and amounts of fluids administered prior to NE.

5.6 Missing data

Missing data will be presented as numbers and percentages. The primary analyses will be based on available data. If the percentage of missing outcome data is >5% we will perform a best-case-worst case analysis as a secondary analysis.

6 **Data handling**

6.1 Data collection

Local investigators or their delegates will collect data from routine source data (medical records and laboratory reports.

6.2 *Data management and quality control*

eCRFs will be securely stored using the REDCap electronic data capture tool, hosted by Karolinska Institutet. REDCap is a secure, web-based software that ensures data accuracy and completeness through automated checks and validation tools. A detailed clinical management plan will be provided to all investigators, outlining procedures for data entry, management, and quality control. Investigators will be assigned two-factor authentication for secure eCRF access. Data analysis will commence only after a thorough validation of the database.

6.3 Study record retention

All research data will be stored securely and confidentially for a minimum of 10 years post-publication at the Department of Anesthesia and Intensive Care, Danderyd

Hospital. Access to the data will be restricted to the primary investigators. Upon request, local and national investigators may access data from their respective sites.

7 Administrative aspects

7.1 Confidentiality

All obtained data and patient-related information will be held strictly confidential by all participating investigators, research staff, and sponsoring institutions. Each site will have access only to its own site-specific participant data. To ensure patient confidentiality, each participant will be assigned a unique subject identification number. All data shared outside the site will be de-identified using this number. Data will be handled and stored in compliance with Swedish data protection regulations.

7.2 Ethical consideration

This study is purely observational and does not influence patient care or treatment.

Septic patients are generally temporarily decapacitated to give informed consent due to their present illness. We therefore would like to include all patients with sepsis and hypotension, assuming consent. There will be information about the study posted in all wards where patients are included and treated (emergency ward, intermediary care, intensive care) with the opportunity to opt out of the study. The study will adhere to the ethical standards outlined in the Declaration of Helsinki (2013).

7.3 Approvals

This study will apply to the Ethical Review Board in Sweden.

7.4 Benefit and risks

The participants will not benefit from being included in the study. The study does not intervene in current practice so there will be no risks of being included.

7.5 Financial disclosures

All financial disclosures from the authors will be declared.

8 Publication policy

The study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBES) guidelines (7). The study protocol and all results, regardless of significance, will be submitted to peer-reviewed medical journals for publication.

9 Authorship

Emergency wards will be granted one authorship per 50 included patients.

10 Conclusion

The time to NE initiation in Swedish hospitals remains unstudied prospectively, representing a significant knowledge gap. Characterizing this time interval is crucial for informing the design and implementation of future studies investigating the optimal timing of NE administration.

11 References

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