Study protocol - Norepinephrine administration through a midline catheter in an intermediate care unit - a retrospective study of complications and patient outcomes.

List of abbreviations
ML = Midline catheter
NE = Norepinephrine
ICU = Intensive Care Unit
IMCU = Intermediate Care Unit
CVC = central venous catheter
PVC = peripheral venous catheter
COPD = chronic obstructive pulmonary disorder

Principal Investigator, Research Team, and Study site:
Principal Investigator: Gustav Torisson, PhD
Co-investigators: Hannes Hartman, PhD, Marcus Ohlson, PhD, Viktor Månsson, PhD, Hanna Karlsson, Ajnaz Afrasiabi
Contact: gustav.torisson@med.lu.se
Study site: Skåne University Hospital

Research Synopsis
Study title: **Norepinephrine administration through a midline catheter in an intermediate care unit - a retrospective study of complications and patient outcomes.**

Study population: Adult patients with circulatory failure, requiring vasopressor support, treated at IMCUs at Skåne university hospital 2019 - 2023

Study design: Retrospective chart review

Sample size: 500 - 1000

Study Duration: Chart review 6 months, data analysis 2 months

Primary Objective:
1. To determine the occurrence of major complications when norepinephrine is administered in a midline catheter.

Secondary Objectives:
2. To describe minor complications
3. To describe what proportion of patients that received a central line.
4. To describe patient outcomes

Background and rationale

Sepsis is a life-threatening condition with a case fatality rate of 15-30%.(1) The incidence of sepsis is increasing, with the largest increase among the oldest old.(2) Western population projections indicate a substantial increase of the oldest population and it is reasonable to assume an increase in the number of sepsis patients. (3) Many sepsis patients are treated at the highest level of care, in intensive care units (ICUs), and the strain on ICUs may increase substantially due to increased caseloads.

Sepsis treatment consists of antibiotics and supportive treatment (ventilator if respiratory, dialysis if renal etc.).(4-6) Sepsis patients often have circulatory failure, resulting in low blood pressure and poor end organ perfusion. If circulatory failure remains despite fluid resuscitation, the condition is labelled septic shock, with a mortality rate of 40%. Then, guidelines recommend initiating treatment with vasopressors, drugs that increase blood pressure, primarily NE.(1, 4, 5) In recent years, there has been a trend towards reducing the amount of fluids given and to start NE earlier.(7, 8) Thus, there is reason to believe also that an increasing proportion of sepsis patients will be eligible for NE treatment.

Norepinephrine raises blood pressure by making the blood vessels contract.(9) Traditionally, NE administration through a peripheral venous catheter (PVC) has been considered hazardous as the short catheter may be misplaced.(10-12) If NE is distributed in the tissue surrounding the blood vessel, a.k.a. extravasation, the consequences include ulceration, blistering and necrosis.(13) Should this occur, the NE infusion must be stopped, an antidote (regitine) should be given and surgical revision may be needed.(14) The fear for extravasation has meant that NE is traditionally administered through a central venous catheter (CVC, a 15-20 cm long catheter inserted into a large-bore vessel). (15, 16) When a CVC is placed, there is a risk of immediate mechanical complications (arterial puncture, hematoma, pneumothorax). Due to these risks, only a minority of physicians, typically anesthesiologists, are placing CVCs, which could delay vasopressor treatment, putting the patient at risk. (17)

In the last decade, the midline (ML) catheter has seen increased use. A ML catheter is a 8-20 cm long catheter placed in a larger vessel in the upper arm (basilic, brachial or cephalic vein), with the guidance of ultrasound. (18) A few retrospective studies have evaluated the safety of NE administration in ML catheters, including one with 250 participants, of whom 150 received NE. In this study, a 20 cm long ML catheter was used, with a very low complication rate.(19) Since the ML catheter is placed in the upper arm, the risks for immediate complications are much lower than for a CVC. The catheter is placed by a physician or nurse, and it is easier to learn ML placement than CVC placement. Thus, more staff can place midline catheters, enabling NE treatment to be initiated outside of ICUs.

In Skåne university hospital in southern Sweden, patients with circulatory failure requiring vasopressor support have been treated in intermediate care units (IMCUs) since 2019. The IMCU provides an intermediate level of care, with a staffing ratio between the full ICU and a general ward. In these IMCUs, NE has been administered through ML catheters of 10 cm length. These are placed by the IMCUs nurses or physicians. The perception is that this routine has been safe and that it has spared ICU resources, but this has not been studied. Therefore,

the aim of the current study is to evaluate NE administration in ML catheters in the IMCU, regarding safety and patient outcomes.

Objectives and endpoints

Primary Objectives

- To determine the proportion of patients having major complications when NE is administered in a ML catheter in an IMCU.

Secondary Objectives

- To determine the occurrence of minor complications when NE is administered in a ML catheter.
- To determine what proportion of patients that received a central line after a ML catheter.
- To determine patient outcomes

Primary endpoints

Endpoint 1 – Major complication.

A Major complication is defined as *any of* the following:

1. Suspected or confirmed **extravasation** of NE in tissue, defined as the presence of any of the following during NE administration:
    - Symptoms such as pain, pallor, induration, swelling, cold, mottling, blistering or necrosis in the ML area.
    - The use of NE antidote (Regitine / Phentolamine)
    - The need for surgical revision of the area.

2. **Deep vein thrombosis**, defined as a thrombosis in ML vessel or a pulmonary embolism, confirmed by ultrasound or radiology performed within 30 days from ML placement.

3. **Midline-associated bloodstream infection (MLABSI)**, defined as a a primary bloodstream infection (BSI) in a patient that had a central line within the 48-hour period before the development of the BSI.

Secondary Endpoints

- **Minor complication**, defined as either of:
    - Accidental dislodgement of midline catheter (resulting in premature removal)
    - Occlusion of midline catheter (impossible to inject in catheter)
    - Leakage
    - Infiltration of other fluids than NE
    - Other complications (phlebitis, major bleeding, nerve damage, local infection)

- **Central line after ML catheter**: defined as the patient receiving a central line after ML catheter insertion.
- **Patient outcomes**
    - IMCU discharge destination (regular hospital ward or occasionally home / ICU escalation / died in the IMCU)
    - IMCU, ICU, hospital length-of-stay
    - In-hospital mortality

Study design and methodology

This is a retrospective study using chart review as the primary methodology. Skåne university hospital is a 900-bed university-affiliated hospital in southern Sweden. Adult (≥ 18 years) patients who have received NE in ML catheters in an IMCU at Skåne university hospital between 2019 and 2023 will be eligible. Case-finding will be performed through a database query to the regional data-hosting platform. Manual screening will be done to ensure that all episodes fulfil this case definition. The only exclusion criterion is that the patient has actively made the electronic medical record unavailable.

Episodes fulfilling the eligibility criterion will be subjected to chart review, which will be done consecutively. The time that NE is initiated in a midline catheter will be considered the baseline. The chart review will be performed according to a protocol with prespecified definitions, see separate document. Data in the following domains will be collected:

1. **Domain: Background data**
    - Age at baseline
    - Sex
    - Length in centimeters (may be retrieved from earlier hospitalisations)
    - Weight in kilograms (as close to baseline as possible, ± 3 months is ok)
    - Body mass index (derived from length and weight)
    - Home care (no/home care / nursing home)
    - Comorbidities (Admission and Discharge notes will be scrutinized, any mentioning or ICD-10 code will be noted, results as yes/no)
        - Chronic cardiac disease (ischemic heart disease, heart failure, arrhythmias, valve disease or other)
        - Chronic pulmonary disease (COPD, lung fibrosis, asthma, bronchiectasis, other)
        - Chronic renal disease (renal failure, previous transplantation, single kidney, polycystic kidney disease, other)
        - Dialysis (hemodialysis or peritoneal dialysis)
        - Active malignancy (malignancy where treatment or surveillance is still ongoing)
        - Diabetes mellitus (any form)
        - Chronic hepatic disease (cirrhosis, steatosis, untreated hepatitis, other)
        - Autoimmune disease (connective tissue disease, inflammatory bowel disease, neurologic disease, other)

  - Transplantation (solid organ or stem-cell transplantation at any point previously)
  - Previous venous thromboembolism (any deep vein thrombosis, pulmonary embolism)
- Anticoagulant therapy (ongoing treatment before baseline with drugs acting on the venous side – DOAC / Warfarin / LMH, regardless of reason)
- Immunosuppression (ongoing treatment before baseline with a drug from group L01 or L04 in the ATC classification OR steroids in a dose equivalent to 10mg Prednisolone or higher).
- Ceiling of care (a ceiling of care decision, that escalation is not considered beneficial to the patient, documented before baseline or during the period that NE is administered in a ML catheter. None / no ICU Escalation / No Cardio-pulmonary resuscitation).
- Central line at baseline (yes or no. Did the patient have a central line at baseline, e.g., a dialysis catheter or subcutaneous venous port?)

2. Domain: current episode

- Infection yes or no (was an infection / septic shock the main reason for starting NE?)
- Reason for NE initiation (if infection => infection focus, otherwise other reason, e.g., cardiogenic shock, hemorrhage)
- Vital signs (These are from the National Early Warnings Scale (NEWS), taken before baseline, if several the one closest to baseline is noted. These may be registered as a NEWS documentation, in free text in the chart or on the monitoring sheet, the one closest to baseline is chosen). Vital signs include:
  - Respiratory rate, breaths / minute
  - Systolic blood pressure, mmHg
  - Diastolic blood pressure, mmHg
  - Mean arterial pressure (derived from systolic and diastolic)
  - Mental state (A = alert, V = responsive to verbal stimuli, P = responsive to pain, U = unresponsive. Anything except A => altered consciousness)
  - Heart rate, beats per minute
  - SpO2, peripheral oxygen saturation in %
  - Temperature, °C
  - Fever (derived from temperature, if ≥ 38.0)
  - Supplemental oxygen, liters / minute (if HFNC / NIV and FiO2, Liters / minute is estimated from FiO2 (L/m = (FiO2 – 21%) / 4))
- Laboratory values (these are taken before baseline as close to baseline as possible, but could be taken after if within specified limits below)
  - Lactate, mmol/L (ok up to 2 hours after baseline)
  - Creatinine, umol/L (ok up to 12 hours after baseline)
  - C-reactive protein mg/L, (ok up 24 hours after baseline)
- Acute kidney injury (yes/no, yes if creatinine > 100 umol/L and no chronic kidney disease)
- Blood cultures taken at baseline (yes/no, yes if cultures are taken within ±48 h of baseline, signalling the suspicion of infection)

- Baseline blood culture results (name of species after contamination removal, as specified before).(20)

3. **Domain Midline** (this is taken from the specific midline note in the charts)
   - ML in date (date of midline insertion)
   - ML side (left or right arm)
   - ML model (name of midline model used)
   - ML diameter (in G, 18G or 20G, later converted to mm or Fr)
   - ML vein (basilic, brachial, or cephalic vein)
   - ML out date (date om midline removal)
   - ML dwell time, days (derived from in and out dates)
   - Number of ML (was another ML inserted after the "index" ML?)

4. **Domain NE**
   - NE start datetime (the date and time that NE was started in a ML = baseline)
   - NE stop datetime (the date and time that NE was stopped in ML, either due to no further need for NE or due to ICU escalation and CVC insertion (in this situation, we presume that NE infusion is switched to CVC if not documented otherwise))
   - NE duration, hrs (the difference between start and stop. If NE has been paused and then restarted, the pause is manually subtracted)
   - NE max dosage, ug x kg^{-1} x min^{-1} (the highest dose of NE given in ML)

5. **Domain Complications**
   - Extravasation (yes or no, any mentioning of extravasation, infiltration, pain, induration, swelling, pallor, cold, mottling, blistering, necrosis in the midline area. Any use of antidote (phentolamine / Regitine) or need for surgery in the midline area. Everything written in charts between NE start and NE stop is scrutinized. In addition, the charts are queried using all the above terms).
   - Deep venous thrombosis (yes or no. If an ultrasound / radiology has demonstrated a deep vein thrombosis in the midline area, from ML in date and up to 30 days after. Also, pulmonary embolisms on CT or scintigraphy without any other explanation)
   - Catheter-related bloodstream infection (yes or no. Is there a positive blood culture taken from ML in date to ML out date + 7 days, with primary growth that is not explained by another infection?)
   - Any major complication (yes or no, derived from above, any of extravasation, thrombosis, or catheter-related bloodstream infection)
   - Minor complications (infiltration (of other medication than NE), dislodgement, leakage, phlebitis, local infection, occlusion of catheter, or other such as bleeding, skin reaction to dressing etc. This should be documented in the midline documentation, but free text will also be scrutinized, including queries for terms above)
   - Premature removal of ML (yes or no. Was the ML prematurely removed (as in before the need for an intravenous access was over) due to a complication)
   - CVC after ML (yes or no. Did the patient receive a central line after ML in date?)

6. **Domain patient outcomes**
    - IMCU discharge date
    - IMCU Length-of-stay (IMCU discharge date – baseline)
    - IMCU discharge destination (regular ward / icu escalation / deceased in IMCU)
    - ICU discharge date
    - ICU Length-of-stay, days
    - Hospital discharge date
    - Hospital Length-of-stay, days
    - In-hospital mortality (yes / no)
    - Final diagnosis (the primary ICD-10 diagnosis at hospital discharge)

Study population

The study population consists of all adults receiving NE in ML catheters in an IMCU in Skåne university hospital between 2019 and 2023. The majority of these will have septic shock, defined as an infection with hypotension that does not respond to fluid therapy in the intended way. The outcome in the group with septic shock will be described separately, for comparison with other settings.

Study Duration/ Study Timeline:

Stage 1: Review of medical records 2-3 months
Stage 2: Data synopsis and analysis 1-2 months
Stage 3: Presentation and publication 1-2 months

Statistical Analysis Plan:

For the primary endpoint any major complications, only descriptive statistics will be used, i.e., the percentage of episodes with major complications. For extravasation, both the proportion of episodes with extravasation (percentage total) will be estimated, as well as events per 1000 treatment-hours (with NE in ML). For deep vein thromboses, the percentage total and events per 1000 catheter-days will be described. For catheter-related BSI, the percentage total and events per 1000 catheter-days will be described.

We hypothesize that the proportion with major complications will be small and that no comparative statistics will be feasible to determine risk factors for complication.

For secondary endpoint minor complications, only descriptive statistics will be used.

Sample size determination

Two previous studies have examined complications when NE is administered through ML catheters, with 1 in 150 and 0 of 238. Thus, as complications seem rare and the focus is purely descriptive, we performed no power calculation but aimed to include as many patients as possible.

Informed Consent Process

In this retrospective chart review, no informed consent will be sought. We hypothesize that 30-40% of eligible participants will be deceased, due to the severity of the condition of interest. The study was approved by the Swedish Ethical Review Authority (Nr: 2022-06476)

Privacy and confidentiality

A unique patient identifier will be kept on an encrypted and password protected separate hard drive, with only a study identification number / code.

The code will then be stored together with clinical data from the medical records, on a separate encrypted hard drive. These will be stored in a locked office and maintained for 10 years after the completion of the study. All source data is maintained by Region Skåne as well, no new data will be collected in the study.

Risk/Benefit:

The only risk for participants is the risk of integrity breach. This will be minimized through data protection routines, as stated above. There will be no individual benefit, but the study will provide better understanding regarding NE administration through ML catheters. This could improve treatment for septic shock, a critical condition with high mortality and an increasing caseload.

Conflict of Interest:

None of the investigators report any conflicts of interest.

Publication and Presentation Plans:

Results will be compiled and sent for consideration to a scientific journal in start of 2024.

References:

1. 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. Critical Care Medicine. 2021;49(11):e1063-e143.
2. Lee S-H, Hsu T-C, Lee M-tG, Chao CC-T, Lee W-C, Lai C-C, et al. Nationwide Trend of Sepsis: A Comparison Among Octogenarians, Elderly, and Young Adults. Critical Care Medicine. 2018;46(6):926-34.
3. Population Projection, Sweden 2021-2070 [Internet]. 2022.
4. Angus DC, van der Poll T. Severe Sepsis and Septic Shock. New England Journal of Medicine. 2013;369(9):840-51.
5. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. The Lancet. 2018;392(10141):75-87.

6. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016;353:i1585.
7. McIntyre LA, Marshall JC. Intravenous Fluids in Septic Shock — More or Less? New England Journal of Medicine. 2022;386(26):2518-9.
8. Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. New England Journal of Medicine. 2022;386(26):2459-70.
9. Girbes AR, Beishuizen A, Strack van Schijndel RJ. Pharmacological treatment of sepsis. Fundam Clin Pharmacol. 2008;22(4):355-61.
10. Ricard J-D, Salomon L, Boyer A, Thiery G, Meybeck A, Roy C, et al. Central or Peripheral Catheters for Initial Venous Access of ICU Patients: A Randomized Controlled Trial. Critical Care Medicine. 2013;41(9):2108-15.
11. Tran QK, Mester G, Bzhilyanskaya V, Afridi LZ, Andhavarapu S, Alam Z, et al. Complication of vasopressor infusion through peripheral venous catheter: A systematic review and meta-analysis. The American Journal of Emergency Medicine. 2020;38(11):2434-43.
12. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. Journal of Critical Care. 2015;30(3):653.e9-.e17.
13. Kahn JM, Kress JP, Hall JB. Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. Critical Care Medicine. 2002;30(8):1899-901.
14. Reynolds PM, MacLaren R, Mueller SW, Fish DN, Kiser TH. Management of extravasation injuries: a focused evaluation of noncytotoxic medications. Pharmacotherapy. 2014;34(6):617-32.
15. Parienti J-J, Mongardon N, Mégarbane B, Mira J-P, Kalfon P, Gros A, et al. Intravascular Complications of Central Venous Catheterization by Insertion Site. New England Journal of Medicine. 2015;373(13):1220-9.
16. Smith RN, Nolan JP. Central venous catheters. Bmj. 2013;347.
17. 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;18(5):532.
18. Adams DZ, Little A, Vinsant C, Khandelwal S. The Midline Catheter: A Clinical Review. The Journal of Emergency Medicine. 2016;51(3):252-8.
19. Prasanna N, Yamane D, Haridasa N, Davison D, Sparks A, Hawkins K. Safety and efficacy of vasopressor administration through midline catheters. Journal of Critical Care. 2021;61:1-4.
20. Ljungquist O, Blomstergren A, Merkel A, Sunnerhagen T, Holm K, Torisson G. Incidence, aetiology and temporal trend of bloodstream infections in southern Sweden from 2006 to 2019: a population-based study. Euro Surveill. 2023;28(10).