The ANDROMEDA-SHOCK TRIAL

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Key Article

Hernandez G, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock. The ANDROMEDA-SHOCK randomized clinical trial. JAMA. 2019; epub ahead of print.

Study Background

- Early resuscitation a key factor to limit progression to MODS and death in patients with septic shock
- Shock is characterized by increased serum lactate levels and signs of tissue hypoperfusion including abnormal peripheral perfusion
- SSC proposes to guide hemodynamic resuscitation by repeated measurement of lactate every 2 to 4 hours until normalization
- Hyperlactatemia may be related to causes other than tissue hypoperfusion, lactate kinetics is relatively slow, and measurements of lactate levels may not be universally available
- Observational studies shown that persistent abnormal peripheral perfusion after resuscitation is associated with organ failure and mortality
- Capillary refill time - easy-to-use resource-independent method to assess peripheral perfusion; rapidly responds to resuscitation

Study Objective

- Compare a peripheral perfusion targeted resuscitation to lactate level targeted resuscitation in patients with early septic shock

Study

- Multicenter, randomized clinical trial
- 28 hospitals in 5 countries (Argentina, Chile, Colombia, Ecuador, Uruguay)
- Patients
    - Consecutive adult patients (>= 18 years of age)
    - Septic shock (defined as suspected or confirmed infection plus lactate >= 2 mmol/L and requirements of vasopressors to maintain MAP >= 65 mm Hg after an IVF bolus of at least 20 ml/kg over 60 minutes)

    - Admitted to an ICU
    - Recruited within 4 hours after fulfilling criteria
- Excluded bleeding, severe ARDS, and DNR
- Randomly allocated to a peripheral perfusion-targeted resuscitation or a lactate level-targeted resuscitation
- Interventions
    - Period was 8 hours
    - CRT
        - Measured by applying firm pressure to the ventral surface of the R index finger distal phalanx was a glass microscope slide
        - Pressure increased until skin was blank and maintained for 10 seconds
        - Time to normal skin color recorded with a chronometer
        - CRT > 3 seconds abnormal
    - Lactate assessed every 2 hours; CRT assessed every 30 minutes; until normalization and then every hour during the intervention period
    - Goal CRT - normalize CRT
    - Goal lactate - normalize or decrease levels by 20% every 2 hours
    - First step
        - Assess fluid responsiveness - each center used its standard technique - followed by fluid challenges with 500 ml of crystalloids every 30 min in responders until goal was achieved
        - In patient who could not be assessed for responsiveness, fluids were continued until the goal was met or safety limit reached
    - Second step
        - In patients with chronic hypertension, if the previous interventions did not meet the goals, a vasopressor test was conducted, transiently increasing norepi until reaching a MAP of 80-85 mm Hg, followed by reassessment of CRT or lactate after 1 to 2 hours
        - If goal was met, the MAP was maintained throughout the intervention period
        - If not, norepi dose was decreased to previous dose and moved to next step
    - Third step
        - Inodilator test
        - Low dose dobutamine or milrinone if target was not reached
        - CRT and lactate reassessed every 1 to 2 hours
        - If end points were not met or a safety issue arose, the inodilator was discontinued
- Primary Outcome - all-cause 28-day mortality
- Secondary Outcomes
    - Death in 90 days
    - Organ dysfunction during the first 72 hours
    - Mechanical ventilation free days within 28 days
    - Vasopressor free days within 28 days

    - ICU and hospital LOS
- Tertiary Prespecified exploratory outcomes
    - Resuscitation fluids during the intervention period
    - Total fluid balance within 8, 24, and 72 hours
    - Occurrence of IAH within 72 hours
    - RRT within 28 days
    - In-hospital mortality
- Statistical Analysis
    - Plan to enroll 420 patients to detect a reduction in 28-day mortality from 45% to 30%

Results

- 424 patients were enrolled
    - 212 assigned to each group
    - All patients included in the ITT analysis for primary outcome
    - Baseline characteristics similar
    - 71% admitted from the ED; 17% from wards, 7% from step-down units, 5% from OR
- Adherence to protocol
    - 13.7% of patients in the peripheral perfusion group
    - 10.8% in the lactate group
    - Most were protocol deviations and 8 patients did not receive the assigned intervention
- Resuscitation, Perfusion, and Hemodynamic Variables
    - Fluid responsiveness
        - 57% were fluid responsive at baseline
        - 25% fluid unresponsive at baseline
        - 18% could not be determined
        - PPV and PLR with VTI most common methods used
    - Fewer patients in the CRT group required a vasopressor test (28.8% vs. 40.1%)
    - 15.6% of patients received a inodilator test
    - Lactate levels significantly lower at 48 and 72 hours in the CRT group (mean difference -0.36); no statistical difference at 2, 4, 8, and 24 hours
    - CRT values significantly lower at 4, 8, and 24 hours in the CRT group (-0.45 seconds), with no statistical difference at 2, 48, and 72 hours
- Primary Outcome
    - CRT: 34.9%
    - Lactate: 43.4%
    - HR 0.75, CI 0.55-1.02; p=0.06
- Secondary Outcomes
    - Less organ dysfunction at 72 hours in the CRT group (SOFA -1.00)
    - No differences in the other 6 outcomes
- Tertiary

- Patients in the CRT group received less fluids within the first 8 hours (-408 ml; CI -705 to -110)

Limitations

- Non-blinded
- Study may have been underpowered to exclude a clinically meaningful difference between groups
- Inter-rater variability for CRT was not evaluated
- Randomization not stratified by sites
- ICU-based study

Author's Take Home Point

- A resuscitation strategy targeting normalization of CRT compared with lactate did not reduce all-cause 28-day mortality