Effects of restricting intravenous fluids vs. standard care fluid therapy in patients with septic shock

The Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) Trial

Abstract

- Background. Septic shock is common, often lethal, costly, and associated with prolonged suffering among survivors and relatives. Traditionally, intravenous (IV) fluids are used to optimise the circulation, and the use of higher volumes is recommended by international guidelines. There is, however, no high-quality evidence to support this. In contrast, data from cohort studies, small trials and systematic reviews in sepsis and large trials in other settings and patient groups suggest potential benefits from restriction of IV fluids in patients with septic shock.
- Objectives. We aim to assess the benefits and harms of IV fluid restriction vs. standard care on patient-important outcome measures in adult intensive care unit (ICU) patients with septic shock.
- Design. CLASSIC is an international, multicentre, parallel-grouped, open-labelled, centrally randomised, stratified, outcome assessor- and analyst-blinded trial.
- Inclusion and exclusion criteria. We will screen all adult ICU patients who have septic shock defined according to the Sepsis-3 criteria and have received at least 1 L of IV fluid (crystalloids, colloids or blood products) in the 24-hours before screening. We will exclude patients who have had septic shock for more than >12 hours at the time of screening, who have life-threatening bleeding, or acute burn injury >10% of the body surface area, who are pregnant and those in whom consent cannot be obtained as per the model approved for the specific site.
- Experimental intervention. In the IV fluid restriction group no IV fluids should be given in the ICU unless extenuating circumstances occur, including signs of severe hypoperfusion, overt fluid loss or a failing GI tract with a total fluid input of less than 1 L per day. In these circumstances, IV fluid may be given in measured amounts.
- Control intervention. In the standard care group there will be no upper limit for the use of IV fluids.
- Outcomes. The primary outcome is 90-day mortality; secondary outcomes are serious adverse events in the ICU (ischemic events or severe acute kidney injury); days alive without life support at day 90; days alive and out of hospital at day 90 and mortality, health-related quality of life and cognitive function at 1-year.

- Trial size. We will randomise 1554 participants to allow the detection of a 15% relative risk reduction (7% absolute) in the restrictive vs. standard care group in 90-day mortality with a power of 80%.
- Timeline.
  - Primo 2018 Authority approvals in DK
  - Medio 2018 1st participant randomised in DK and authority approvals elsewhere
  - Primo 2019 1st interim analysis
  - Medio 2019 2nd interim analysis
  - Ultimo 2019 3rd interim analysis
  - Medio 2020 Last participant randomised
  - Ultimo 2020 Primary report on 90-day outcomes submitted.
  - Medio 2021 Last participant followed for 1 year
  - Ultimo 2021 Long-term outcome report submitted

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