

Temporal changes in plasma Lactate concentration in ICU
Patients with Septic Shock randomised to Intravenous Fluid
Restriction – a sub-study of the CLASSIC RCT

NCT05629780

2022-12-28

Temporal changes in plasma Lactate concentration in ICU Patients with Septic Shock randomised to Intravenous Fluid Restriction – a sub-study of the CLASSIC RCT

Amendment: Updated Statistical Analysis Plan

Trial hypotheses and outcomes

The objective of this sub-study of the CLASSIC trial is to use the randomisation to restrictive or standard IV fluid therapy to study temporal changes of lactate and time to resolution of hyperlactatemia.

Research questions:

1. Do lactate values differ between the two intervention groups in terms of:
 - a. Differences in time to resolution of hyperlactatemia (defined as plasma lactate <2 mmol/L), ICU discharge and death.
 - b. Temporal changes in lactate concentrations over time (based on all available plasma lactate analyses during the first 72 hours from randomisation).
2. Same question as 1.a. above but comparing patients with a highest baseline (= the 3 hours leading up to randomisation) lactate of >4 mmol/L vs ≤4 mmol/L.

Hypotheses:

1. Restrictive IV fluid will not significantly affect the time to resolution of hyperlactatemia compared with standard IV fluid.
2. Patients with baseline lactate >4mmol/L will not reach resolution of hyperlactatemia faster with standard IV fluid compared with restrictive IV fluid.

Primary outcome

Time to first resolution of hyperlactatemia within 72 hours after randomisation.

Resolution of hyperlactatemia is defined as a plasma lactate value <2mmol/L. We will assess the time from randomisation to the first occurrence of a lactate value <2mmol/L irrespective of subsequent changes in the 72 hours after randomisation.

Method and design

All available serial time-stamped point-of-care blood gas analyses from patients included in the CLASSIC trial will be retrospectively collected and analysed for the first 72 hours after randomisation or until death or discharge from the ICU, whichever comes first.

The full baseline patient characteristics of the sub-study cohort (age, sex, pre-existing co-morbidities (haematological or metastatic cancer, ischemic heart disease, chronic hypertension and long-term dialysis), time from hospital/ICU admission to randomisation, the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU) [1] and predicted 90 day mortality, source of ICU admission, focus of infection, bodyweight, highest plasma lactate, highest dose of norepinephrine, volume of IV fluid 24 hours before randomisation, use of

systemic corticosteroids, highest creatinine and use of respiratory support) will be presented in Table 1. Categorical variables will be summarised as N (%) and continuous as median (IQR); if more informative, very skewed continuous variables will be binned and reported as ordinal ones. Cumulative fluid volumes and balances for days 1 through 3 will be presented in Table 2. Outcome data will be presented in Table 3. These data will be collected from the CLASSIC RCT trial database.

We will produce a descriptive graph (Figure 1), depicting medians of lactate values over time with interquartile ranges for the two treatment arms, inspired by figure 1 in the post-hoc analysis of the CLASSIC feasibility trial by Hjortrup et al [2].

Time to resolution of hyperlactatemia will be modelled with a competing risks regression model adjusting for stratification variables (site/centre, hematologic/metastatic malignancy), SMS-ICU Score, focus of infection (urinary tract focus versus other foci), and use of systemic corticosteroids; the same covariates were used in the adjusted analysis of the primary outcome in the large CLASSIC trial [3,4]. Death and discharge will be competing outcomes, and administrative censoring imposed 72 hours after randomisation. The significance levels for the analyses of research questions 1.a and 2 will be 5% and 1%. Figure 2 will visualise the cumulative incidence (%) over the first 72 hours post-randomisation of resolution of shock, discharge and death, stratified by allocation group.

Sample size estimate

The estimated sample size will comprise 777 patients consisting of 129 Swedish patients, 599 Danish patients (Capital Region and Region Zealand), and 49 Czech patients.

1. Granholm A *et al*, Simplified Mortality Score for the Intensive Care Unit (SMS-ICU): protocol for the development and validation of a bedside clinical prediction rule, *BMJ Open* 2017;7: e015339. doi: 10.1136/bmjopen-2016-015339
2. Hjortrup PB *et al*, Effects of Fluid Restriction on measures of circulatory efficacy in adults with septic shock. *Acta Anaesthesiol Scand* 2017 Apr;61(4):390-398
3. Meyhoff TS *et al*. Restriction of Intravenous Fluid in ICU Patients with Septic Shock (CLASSIC). *NEJM* 2022 Jun;386(26):2460-2470
4. Meyhoff TS *et al*. Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial- Protocol and statistical analysis plan. *Acta Anaesthesiol Scand*. 2019 Oct;63(9):1262-1271.