RCoA Research, Education & Travel Grants 2016

Award: The Ernest Leach Research Fund

Applicant: Dr Jon Silversides, Belfast Health & Social Care Trust

Project Title: *Role of Active Deresuscitation After Resuscitation-2*

Project Description:

Background and importance of the research question

In patients who are critically ill, accumulation of fluid is common due to both administration of intravenous fluid, medications and nutrition, and to impaired excretion. This fluid accumulation is consistently associated with worse outcomes including mortality in observational studies, although the extent of residual confounding is unclear.

In a recent systematic review and meta-analysis, we found limited low-quality evidence for improved clinical outcomes with a conservative rather than a liberal fluid strategy or usual care in the post-resuscitation phase of critical illness, while in a recent survey of over 500 intensivists, we found wide variation in attitudes and self-reported practices with regard to fluid strategies, and widespread support for clinical trials comparing a conservative fluid strategy (restrictive fluid administration and removal of accumulated fluid) to usual care.

Fluid accumulation increases venous pressure which reduces blood flow through capillary beds and may induce endothelial glycocalyceal shear injury. This may exacerbate leakage of fluid from capillaries and tissue oedema, impairing diffusion of oxygen to cells. Our hypothesis is that in critically ill patients, a conservative fluid strategy reduces cellular hypoxia and injury, allows more rapid repair of the endothelial glycocalyx, reduces inflammation, improves organ function, and ultimately reduces mortality.

Methodology

We plan to undertake a 100-patient randomised controlled trial of a conservative fluid strategy compared to standard care in patients with critical illness. The primary outcome will be feasibility, with secondary clinical and biological endpoints.

We intend to measure levels of relevant biomarkers at baseline and at days 4 and 7 of conservative fluid management or usual care to investigate mechanistic aspects of our overall hypothesis. These biomarkers will include Interleukin-6 (IL-6), and C-reactive protein, widely used biomarkers of inflammation, in order to assess whether a conservative fluid strategy reduces inflammation compared with usual care. We also intend to measure plasma levels of Angiopoietin-2 (Ang-2) and Syndecan-1, biomarkers of endothelial dysregulation and glycocalyceal injury respectively which are elevated in critical illness states, hypothesising that levels will normalise more rapidly with conservative fluid management than with usual care. Furthermore, we

wish to compare the change from baseline plasma levels of Neutrophil Gelatinase-associated Lipocalin (NGAL), a biomarker of acute kidney injury, to test the hypothesis that NGAL levels will decline more rapidly with conservative fluid management than with usual care. The aim is to provide insights into the mechanisms by which fluid strategies may influence clinically important outcomes in critical illness states.

Timescale and justification of funding

We are seeking support for the purchase of ELISA (Enzyme-linked Immuno-Sorbent Assay) reagant kits and laboratory consumables for the analysis of IL-6, Ang-2, Syndecan-1 and NGAL levels in plasma. Blood sampling will be undertaken alongside other aspects of routine care and trial-specific procedures. Samples will be frozen and stored, and analysis will be undertaken with the assistance of laboratory technical staff at Queen's University of Belfast. It is hoped that enrolment will take place over 18 months in 2 intensive care units from July 2017 to December 2018.