Study Protocol
(including Statistical Analysis plan)

Title

- Does the use of LiDCOplus alter decision-making in fluid prescription during resuscitation in the Intensive Care Unit?

Or Use of LiDCOplus in Fluid Resuscitation Decision-Making

Introduction

- Rationale

  Unwell patients in the intensive care unit (ICU) often need supplementary fluids to be given into the bloodstream through a drip in a vein (venous cannula), however too much fluid can be harmful. It can sometimes be difficult to tell whether or not a patient will benefit from extra fluids so they are given a "fluid challenge", whereby a small volume of fluid is given quickly into the cannula and the change in their status is noted. If the patient's condition improves, this suggests that the patient is "fluid responsive" and needs more fluid.

  A LiDCOplus cardiac output monitor is a device used in the ICU to estimate the amount of blood ejected from the heart on each heartbeat using pressure readings obtained from a tube placed in one of the patient's arteries (arterial line).

  We aim to determine whether or not the use of this device called makes a difference to the judgement of "fluid responsiveness" when the patient is given a fluid challenge when compared to simply using measurements of pulse and blood pressure and assessing the circulation in the patient's limbs. This will allow us to determine whether or not the LiDCOplus cardiac output monitor alters the decisions made by doctors and nurses about how much fluid to give their patients and hence if it is of any benefit.

- Background information including literature review

  In the published literature there are multiple studies using the LiDCOplus-derived change in stroke volume as a gold standard of fluid responsiveness against other measures such as stroke volume variation and pulse pressure variation[1,2]. However there do not seem to be any studies evaluating the change in stroke volume itself as a measure of fluid responsiveness against clinical parameters, as proposed in the current study.

  There are two studies which compare outcomes in patients whose fluid therapy was guided by LiDCO vs controls. One was a pilot study of 21 severely burned adults which compared fluid therapy in patients with and without LiDCO monitoring and showed that the LiDCO group received significantly less fluid[3]. The other was a study on intra-operative patients undergoing surgical repair of fractured neck of femur under spinal anaesthetic[4] and is not relevant to the critically unwell patients in the intensive care unit we wish to study.

  There does, therefore, appear to be a lack of current evidence to address the research question and further research in to this area would be desirable.

- Potential risk and benefits

The results of this study should benefit patients in ICU by evaluating the usefulness of a piece of equipment used regularly to guide patient care. If it is shown to be useful, this may encourage its use in order to gain maximum benefit for patients. If it is shown not to be useful, this may lead to a reduction in its use and subsequent cost savings to ICU departments which can use the extra money to improve patient care in other areas.

There is minimal potential for direct benefit to patients as the research does not involve any change to their standard monitoring and treatment. However, there may be a benefit in the special attention paid to the patients' response to fluids e.g. minimising errors and picking up additional information from the patient's assessment.

There are minimal potential risks for research participants as their monitoring or treatment will not be affected apart from a very brief delay while the clinician fills out the research proforma by the bedside.

- Prior experience of intervention

  The LiDCOplus device is widely used in the authors' intensive care unit to guide fluid therapy in patients requiring fluid resuscitation. It is thought that this allows administered fluid volumes to be tailored to maximize benefit and minimise harm to the patient it is not entirely clear from clinical experience whether or not this is the case.

- Study Hypothesis

  The Null Hypothesis is there is no difference to the judgement of "fluid responsiveness" using information from a LiDCOplus monitor when a patient is given a fluid challenge, when compared to simply using standard clinical measurements of responsiveness.

Aim/Primary and Secondary Objectives

- **Primary Endpoint**
  To determine whether or not use of the LiDCOplus cardiac output monitor results in an estimate of a patient's response to a fluid challenge which is significantly different to that simply obtained using standard measures of blood pressure, heart rate and limb circulation.
- **Secondary endpoints**
  [None]

Methodology

A patient undergoing fluid resuscitation guided by a LiDCOplus device will have a research data pro forma left at their bedside along with instructions on how to complete it. When a patient is given a fluid challenge (the fast intravenous administration of 250ml of Hartmann's solution) as part of their routine management, a number of additional actions will take place. The screen of the LiDCOplus will be covered up initially and baseline heart rate, blood pressure and subjective assessment of limb circulation will be recorded on the proforma. After the fluid challenge is administered the above observations will be recorded again and at this point an assessment of whether the patient is "responsive" or "unresponsive" will be made. The LiDCOplus screen will then be uncovered and the change in stroke volume will be recorded (the cut off for being fluid responsive is a change of >10%). Finally, an overall decision regarding fluid responsiveness is made and recorded, along with the grade of decision maker (e.g. staff nurse or consultant).

This observational study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

Study Population

The study population will be a convenience sample as appropriate to the study type so the exact number of participants is not known as yet.

We aim to include all patients undergoing fluid resuscitation using a LiDCOplus cardiac output monitor in Glasgow Royal Infirmary Intensive Care Unit during the study period.

The researchers will regularly review the patients on the ICU to identify suitable participants.

Inclusion criteria

- Adult patients
- Admitted to Intensive Care Unit (ICU)
- Undergoing fluid resuscitation guided by fluid challenges
- Monitored by a LiDCOplus cardiac output monitor attached to an arterial line

Exclusion criteria

- Poor arterial line trace
- Moribund state
- Patient / relative refusal
- Contra-indication to fluid bolus

Identification of participants and consent

All eligible patients as per the inclusion and exclusion criteria will be identified and included in the study, which will simply involve a single-sheet pro forma being placed at their bedside for the clinical staff to complete when the patient undergoes a fluid challenge.

The direct care team will carry out the data gathering by completing the pro forma and the research team (who are part of the clinical team) will also be involved to remind the rest of the clinical team about the study and ensure any questions are answered.

Given that the patients will not experience any difference in their care but the clinical staff will have to perform some extra steps when administering a fluid challenge, it is the clinical staff (nurses and doctors) involved who will be asked for their informed consent to take part in the study.

Study Outcome Measures

4.1 Primary Outcome Measure

Proportion of decisions about fluid management changed by knowledge of the change in stroke volume post fluid challenge, as derived by LiDCO cardiac output monitor.

4.2. Secondary Outcome Measure

None

Statistics and Data Analysis

As this is a descriptive study only descriptive statistics will be used, i.e. the proportion of patients deemed fluid-responsive by the use of LiDCOplus versus standard parameters alone and the proportion of fluid responsiveness decisions altered when the information from the LiDCOplus is taken into account.

STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when the planned sample size has been achieved.

Protocol Amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TSC and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The CI and the TSC will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office(s).

Ethics

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh[2000]).

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this study.

The CI will be responsible for updating the Ethics committee of any new information related to the study.

Finance and Indemnity

NHS employed researchers will be covered for negligent harm through the NHS CNORIS indemnity scheme. If you are a University employee you may need extra cover for non-negligent harm through your University. Please check this with your Research and Enterprise department.

The study is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

Publications

Study results whether, negative or positive, should be disseminated. Details of your plan for dissemination should be included here.

Reference

1. MacDonald N, Ahmad T, Mohr O, Kirk-Bayley J, Moppett I, Hinds CJ, Pearse RM. Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: an observational substudy of the OPTIMISE trial. Br J Anaesth. 2015 Apr;114(4):598-604

2. Drvar Z, Pavlek M, Drvar V, Tomasević B, Baronica R, Perić M. [Stroke volume and pulse pressure variation are good predictors of fluid responsiveness in sepsis patients]. Acta Med Croatica. 2013 Dec;67(5):407-14.

3. Tokarik M, Sjöberg F, Balik M, Pafcuga I, Broz L.Fluid therapy LiDCO controlled trial-optimization of volume resuscitation of extensively burned patients through noninvasive continuous real-time hemodynamic monitoring LiDCO. J Burn Care Res. 2013 Sep-Oct;34(5):537-42.

4. Moppett IK, Rowlands M, Mannings A, Moran CG, Wiles MD; NOTTS Investigators. LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: a randomized trial and systematic review. Br J Anaesth. 2015 Mar;114(3):444-59.