

Fluids in Septic Shock (FISSH) Trial
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Project Design, Methodology & Analysis

Research question for the FISSH RCT

In patients with septic shock, what is the impact of administering fluids with higher chloride content (normal saline) compared to solutions with lower chloride content (Ringer's lactate) on acute kidney injury and other patient important outcomes such as 30-day mortality, need for life support and ICU/hospital length of stay?

PICOT Question for FISSH RCT

Population: Adults 16 years or older in the ICU with septic shock.

Intervention: Administration of fluids with a lower chloride concentration while in the ICU

Control: Administration of fluids with a higher chloride concentration while in the ICU

Outcomes: The primary outcome is AKI (assessed using KDIGO guidelines). We will also examine 30-day mortality, need for life support, ICU/hospital length of stay, rates of hyperchloremia, acidosis and hyperkalemia.

Type of study: Randomized, concealed, blinded, parallel-group RCT in Ontario.

Study Design & Study Centers

This is a pragmatic multi-centre stratified concealed parallel-group blinded RCT. The primary outcome for this trial will be acute kidney injury (as assessed by KDIGO guidelines). We also plan a translational biology sub-study examining differences in serum cell-free DNA levels between study arms. We plan to enrol patients at 10 Ontario hospitals. This study will be done with the support of the Canadian Critical Care Trials Group (CCCTG) a network of intensive care physicians and research co-ordinators across Canada who conduct investigator-driven research. The principle investigator and many of the study co-investigators are members of the CCCTG.

Patients

A trained ICU research co-ordinator at each institution will screen all patients for eligibility at the time of ICU admission. On weekends or after-hours ICU clinical staff will perform screening as availability allows. For the 2-centre pilot study¹, both centres were successful in operationalizing after-hours remote (off-site) screening. This was facilitated through close collaboration with the on-call physician and the pharmacy. We plan to apply this model and lessons learned from the pilot to this larger provincial FISSH trial. The research co-ordinator will maintain a screening log at each study center documenting all patients reviewed and reasons for exclusion.

Inclusion and Exclusion Criteria

Inclusion: We will include patients ≥ 16 years of age who meet all of the following: 1) require fluid resuscitation for refractory hypotension (systolic blood pressure < 90 mmHg or mean arterial blood pressure < 65 mmHg after 1 Litre bolus over 1 hour or less) or organ hypoperfusion (serum lactate > 4 mmol/L), 2) have a clinical suspicion of infection; 3) are within 6 hours of hospital admission or critical care response team consultation, and 4) are anticipated to require ICU admission.

Exclusion: Patients will be excluded if they have 1) intracranial bleed or intracranial hypertension during the index hospital admission; 2) $> 10\%$ of body surface area acute burn

injury; 3) bleeding/hemorrhage as likely cause of hypotension; 4) a lack of commitment to life support; 5) been previously enrolled in FISSH or a confounding trial (e.g. a trial examining the effect of other intravenous fluids in septic shock patients; 6) been transferred from another hospital or facility >6 hours since presentation to the first hospital; 7) pre-established ESRD or are receiving hemodialysis (intermittent or continuous) at the time of enrolment; or 8) been admitted to ICU directly from the operating room or post anaesthetic care unit.

Informed Consent

Given the urgency of the intervention, the fact that most patients will not be capable to consent at the time of study entry, and that both the experimental and control study fluids are currently considered the standard of care, we propose a deferred consent model. This model worked well at both of the initial pilot study centres, ensuring timely enrolment and minimizing contamination with non-study fluids. Patients will be enrolled in the study and consent will subsequently be obtained from the patient, the substitute decision-maker (SDM), or both, ideally within 72 hours. There is precedence for using a deferred consent model in studies examining the use of emergency intravenous fluids in Canadian centres². If patients enrolled with deferred consent expire prior to obtaining first person or SDM consent we will use this data. This is again consistent with the approach used in other ICU trials examining low risk interventions.

Allocation & Randomization

Research coordinators will log into the centralized data centre where computerized prompts will request preliminary identifying data. If eligibility criteria are confirmed the patient will be randomly allocated in a 1:1 schedule to either the lower or higher chloride group using undisclosed and variable block sizes to preserve concealment of allocation. Randomization will be stratified by study centre.

We will provide the research pharmacies with a randomization table to expedite delivery of study fluids. This will allow the research pharmacist to prepare the proper fluid for the subsequent patient before they are identified. This will help to avoid up-front contamination with open label fluids. The foregoing steps were successfully operationalized in the 2-site pilot study.

Experimental & Control Interventions

Study fluids will be administered immediately after randomization and continued until discharge from the ICU, or until 30 days after enrolment, whichever comes first. Patients will receive the allocated fluid type for both resuscitation and maintenance infusions. However, blood products and fluids used for medication infusions (including a dedicated medication line up to 20ml/hr) are exempt due to drug-fluid compatibility issues.

Once a patient is enrolled, study personnel will bring blinded infusion bags of study crystalloid fluids found on pre-prepared carts to the patient's bedside. When to administer fluid and the amount to be infused will all be left to the discretion of the treating physician. The ICU clinical team will all be blinded to the chloride concentration of the fluid. This protocol proved feasible at both study sites in the pilot. Normal saline will be used for those randomized to high chloride fluid (chloride concentration 154 mmol/L) while Ringer's Lactate will be used in those in the low chloride arm (chloride concentration 110 mmol/L).

Blinding

Patients, nurses, allied health providers, and physicians will be blinded to study allocation. All study fluids, whether containing a lower or higher chloride concentration will be identical in appearance, consistency and packaging. Bags of saline and Ringer's Lactate look identical and the product label will be covered with opaque study labels or tape. Individual center pharmacists will help ensure patients receive their allocated fluid type and thus, will not be blinded.

We will attempt to keep all clinical staff blinded to a patient's allocated study arm. This will be easier to accomplish in a patient's first few study days (the more crucial period with respect to co-interventions) however unblinding may occur later in the patient's ICU stay secondary to large volume fluid exposure and the resultant changes seen in blood tests. We will also ensure blinding of research staff, site investigators, data collectors, outcome adjudicators, and data analysts. An emergency phone number will be available at all centers should emergent unblinding be required (only in situations where management decisions would depend on knowledge of the chloride content of fluid being administered which is likely very rare; this did not occur during the pilot).

Open Label Fluids

Open label fluid use will represent protocol violation except for management of hypoglycaemia or hypernatremia. In these situations, study fluid infusions may be held and open label fluid may be administered at the discretion of the treating physician until it is deemed safe to resume study fluid. The research coordinator will document all open-label fluid use for the indications mentioned above and will document reasons for any non-adherence. All other aspects of patient care will be left to the discretion of the treating physician.

Outcomes

Primary Outcome

Our primary outcome for the FISSH Trial is development of stage 2 or worse acute kidney injury (AKI) according to KIDGO guidelines³ based strictly on serum creatinine criteria. Stage 2 AKI is defined as serum creatinine 2.0-2.9 times baseline. Stage 3 AKI is defined as creatinine ≥ 3.0 times baseline OR increase in serum creatinine to >353.6 $\mu\text{mol/L}$ OR initiation of renal replacement therapy. For the purposes of analysis, baseline creatinine will be an outpatient reading within 365 days of the current admission date. If multiple pre-hospitalization values are available, the one closest to the date of hospital admission will be used. If an outpatient pre-hospitalization value is not available, the lowest creatinine value obtained during the current hospitalization will be considered the baseline⁴.

Although not patient-important itself, AKI is an important surrogate and an early sign of end-organ damage associated with septic shock⁵. Previous work has demonstrated that renal physiology is affected by serum chloride levels and the choice of intravenous fluid used may influence development of AKI and need for RRT⁶⁻⁹. Also, development of AKI is associated with increased mortality¹⁰⁻¹² and ICU length of stay^{10, 12} in critically ill patients.

Secondary Outcomes

Other measures of acute kidney injury – There are multiple approaches to diagnosing AKI in the critically ill and several guidelines exist. Although our primary outcome is KDIGO stage 2 or worse AKI, we also plan to investigate the incidence of AKI using other criteria including: KDIGO stage 2, KDIGO stage 3, RIFLE¹³, AKIN¹⁴, use of renal replacement therapy within 30 days post randomization and delta peak:baseline creatinine ratio. For all AKI criteria we will only use the serum creatinine criteria. Limited data are available comparing the incidence of AKI using the various definitions^{15, 16}.

Secondary Outcomes – Other secondary outcomes will include: 30-day mortality, hospital/ICU mortality, hospital/ICU length of stay, ventilator free days (censored at 30 days), need for vasoactive agents, incidence of biochemical abnormalities during study period (including hyperchloremia, hyperkalemia, hyponatremia, metabolic acidosis).

Translational Biology Sub-study for Hamilton Sites

Blood will be collected into citrated tubes at the time of enrolment, on Day 2, Day 4 and weekly thereafter while the patient is in the ICU and on study. Within 2 hours of collection the blood will be centrifuged at 1,500 x g for 10 min at 20°C, and the plasma stored as 200 uL aliquots at -80°C and thawed at the time of assays. cfDNA will be isolated from 250 µL of plasma using the QIAamp DNA mini and Blood Mini Kit (Qiagen, Valencia, CA). The concentration of the DNA will be measured by UV absorbance at 260 nm using a spectrophotometer (Beckman DU 7400, Beckman Coulter Inc., Brea, CA). The purity of the DNA will be confirmed by determining the OD₂₆₀/OD₂₈₀ ratio, with pure DNA having a ratio of ~1.9). Total protein C antigen in citrated plasma samples will be quantified by an enzyme immunoassay (Affinity Biologicals Inc., Ancaster, ON).

Feasibility Outcomes

We will examine the feasibility of expanding the FISSH trial to an increased number of sites. Although the pilot met all feasibility thresholds at two sites, the focus of this grant will be on expansion and evaluation of protocol implementation elsewhere. Therefore, we will capture all the feasibility outcomes we used in the pilot, and the results will inform the planned larger national/international FISSH trial powered for mortality. The feasibility outcomes are:

Consent Rate – We will consider the consent rate adequate if greater than 70% of SDMs or patients choose to participate. Research coordinators will receive consent scripts and other consent tools developed by our group¹⁷. Reasons for declining to participate will be recorded. The study steering committee will review the consent rate at least quarterly and, if necessary, implement measures to improve the consent process. Consent rate in the FISSH pilot study was 96%.

Recruitment – Successful recruitment will be defined as achieving enrolment of 200 patients at 10 sites over the 24-month enrolment period. This works out to approximately 1 patient/center/month. If necessary, the steering committee will implement strategies to improve enrolment. Recruitment in the FISSH pilot study was 2.6 patients/site/month.

Protocol Adherence – Successful adherence will be defined as patients receiving at least 75% study fluid of all intravenous fluid that is administered in the ICU excluding blood products and

medication infusions. Pre-study education sessions and routine clinical reminders (including posters, bedside clinical cards and indicators for patient's charts) will be supplied to help improve study compliance. Research coordinators will document all fluid that study patients receive including protocol violations. Reasons for violations will be documented to distinguish deviations for clinical reasons from true protocol violations. Protocol adherence will be evaluated at least quarterly by the steering committee. Protocol violation reports will be sent back to each study site throughout the trial to provide real-time feedback and, if necessary, further behavioural strategies will be employed to improve adherence. Protocol adherence in our FISSH pilot was 94.2%.

Study Data Collection

All CRFs were pre-tested (via the FISSH pilot work) and edited for clarity and ease-of-use prior to the study initiation. Trained research staff at each study centre will collect the data, and will complete paper case report forms (CRFs), which they will transcribe into web-based e-CRFs (REDCap – <http://www.project-redcap.org>) that are encrypted and password-protected. The online database fully complies with FDA and Health Canada rules for electronic data management. Baseline data will include eligibility criteria, baseline demographic data, admitting diagnosis, SOFA score and APACHE II admission prognosis score. No data that could lead to study patient identification will be entered. While patients remain in the ICU, daily data collection will include measures of organ dysfunction (MODS), ventilator requirements, hemodynamics, all fluid administered (including study, non-study and blood products), use of renal replacement therapy, and other daily relevant bloodwork values. Co-interventions will also be captured including but not limited to use of bicarbonate, vasopressors/inotropes, corticosteroids, and diuretics. Vital status will be documented during the 30-day followup period (discharge, readmission, death).

The web-based CRF will allow for data validation, real-time consistency checks and frequent audits of entered data to ensure they are complete and accurate. The paper CRFs will be available as backup or to check potential errors against. The centralized data center will be responsible for managing the database and quality assurance using anomaly searches and logic checks. Immediate data entry will ensure missing data is identified quickly and issues are resolved in a timely manner. Centre staff will initiate inquiries to study centres that are slow to enter data or enter inconsistent data with helpful remediation recommendations offered. Study documents and CRFs will be kept for the duration required by local regulatory bodies. The screening log (maintained by the local research coordinator) will be transcribed to the e-CRF on a daily basis to ensure it is consistent with the information at the centralized data center.

FISSH Sample Size

The baseline risk of AKI in critically ill patients as defined by KDIGO criteria varies in the existing literature from 38-51%¹⁶. As we are enrolling only those patients with septic shock, we expect that the rate of AKI will be at the upper end of that estimate for patients included in the FISSH trial. In our pilot study of 50 patients, 25 (50%) experienced KDIGO Stage 2 or 3 AKI during the study period. To detect a 35% reduction in the relative risk (17% absolute risk reduction) of Stage 2 or 3 AKI (as defined by KDIGO) with the use of low chloride fluid, as compared with high chloride fluid, from a baseline rate of 50%, we determined that 123 patients per group (total 246) would provide a power of 80% with the use of a two-sided alpha level of

0.05. To be conservative, we plan for 250 patients total in the FISSH trial (125 per arm). As 50 patients have already been enrolled in the pilot and will be included in the final analysis, this will require enrolling a further 200 patients.

FISSH Study Analysis Plan

A statistician blinded to study group identification will conduct all analyses based on the intention-to-treat principle. The baseline characteristics comparing low chloride fluid and high chloride fluid groups will be reported using means (and standard deviations), medians (and inter-quartile ranges) or proportions as indicated.

Dichotomous outcomes will be reported using relative risk ratio and 95% confidence intervals and calculated using Cox regression analysis accounting for stratification variables. Non-parametric testing, the Mantel-Cox log rank test, will be used for the continuous outcomes of ICU length of stay, hospital length of stay and ventilator-free days given the data is not normally distributed. These continuous variables will be censored at 30 days. An independent t-test will be used to compare the means of the safety outcomes (serum K, Na, pH) between the 2 groups and mean difference with 95% confidence intervals and p-values will be reported. A p-value of <0.05 will be considered statistically significant for all outcomes. All statistical tests will be two-sided.

Subgroups

An *a priori* subgroup assessment will be done for all outcomes of the larger trial. Three planned subgroups include: patients under 65 years old as compared to patients 65 or older (hypothesized that older patients will benefit more from low chloride fluid); patients with an APACHE II score <25 as compared to those with an APACHE II score of 25 or higher (hypothesized that those that are sicker will benefit more from low chloride fluid); and patients that receive < 2 Litres of fluid pre-randomization as compared to those that receive 2 Litres or more pre-randomization (hypothesizing that those that receive more fluid pre-randomization will show less benefit with low chloride fluids).

FISSH Trial Administration

Dr. Bram Rochwerg, the principle investigator for this trial, will lead the Steering Committee that includes senior and experienced ICU trialists, a trial manager (Peggy Austin), a biostatistician, a data manager from the centralized data center, a transfusion medicine specialist and other local and international experts in ICU research methodology and fluid resuscitation. Current members of the Steering Committee include Drs. Deborah Cook, Maureen Meade, Gordon Guyatt, Michelle Zeller, Sangeeta Mehta, Frederick D'Aragon, and Francois Lamontagne. Drs. Cook, Meade and Mehta are internationally recognized ICU trialists who have led a number of large multinational CIHR funded studies. Dr. Cook has also provided mentorship for 2 other trials of fluid resuscitation^{2, 18}. Dr. Gordon Guyatt is an internationally acclaimed methodologist with extensive RCT expertise. Dr. Francois Lamontagne is a mid-career clinician-investigator with experience running pilot RCTs in the area of resuscitative medicine. Dr. Zeller is a haematologist and transfusion medicine specialist who works with Canadian Blood Services.

Quarterly meetings of the Steering Committee will occur either in person or via teleconference. The Steering Committee will be responsible for monitoring study recruitment and targets,

monitoring issues with data collection and missing data, and making decisions on new center recruitment. Dr. Rochwerg will meet with the trial manager weekly, and will be responsible for overall start-up and study management. Site principle investigators (PIs) have been identified at each center and they will be responsible for all local procedures in conjunction with Dr. Rochwerg. This includes local REB approval, hospital approval, ensuring pharmacy cooperation and ensuring all parties are properly trained. The Steering Committee and central Methods Center staff will closely support local PIs. At the time of center initiation all relevant paperwork and standard operating procedures (SOPs) will be supplied to the local PI. Dr. Rochwerg and the trial manager will provide on-site training sessions for the local PIs and research coordinators on the study protocol and data collection procedures.

Research meetings with all research staff from all centers will be planned at least twice a year with relevant study updates, recruitment numbers and motivational messages. Dr. Rochwerg, or a Steering Committee delegate, will be available 24 hours a day, 7 days a week if a specific center has problems or questions. The FISSH trial has been registered on clinicaltrials.gov (NCT02748382).

FISSH Trial Feasibility

Dr. Rochwerg is a junior faculty member in the Department of Medicine (Division of Critical Care) with a joint appointment in the Department of Health Research Methods, Impact and Evidence. He has a Masters Degree in Health Research Methodology, in which his thesis centered on developing the FISSH research program. He has significant clinical research experience at this early stage and he has assembled an expert Steering Committee to advise and assist him in his role as principle investigator. The Steering Committee for this trial has enormous experience in ICU RCTs and they are fully committed to the FISSH project and to providing intensive support to Dr. Rochwerg. In addition to this prospective research, Dr. Rochwerg has led systematic reviews and meta-analyses, some of which examined the role of fluids in resuscitation^{9, 19, 20}. He is a practicing intensive care clinician and has significant (25 weeks/yr) protected research time to dedicate to completing this trial.

The centers that we plan to recruit to participate in the FISSH trial have all previously participated in trials administered by members of the steering committee and have established research infrastructure and efficient teams. Our methods center has crucial experience gained via the FISSH pilot trial.

Ethical Considerations

The trial will adhere to the Helsinki Declaration and all local and national laws for each participating centre. Most patients will be unable to provide consent at the time of enrolment. Patients will be enrolled using deferred consent; however, patients will only be continued in the trial if they or a their SDM provides consent in a timely manner.

Knowledge Translation

The knowledge translation (KT) plan for the FISSH trial includes both integrated and end-of-grant KT. From an integrated KT standpoint, multi-disciplinary groups at all participating centers (physicians, pharmacists, nurses, etc) will be engaged through email and presentation of research rounds on the importance of this topic and the details of the study planned. A structured abstract

and information poster will be circulated to all participating centers for distribution and posting throughout their center. Practicing clinicians at participating centers will be informally surveyed prior to study initiation to better assess current state of knowledge regarding chloride content of resuscitation fluids and prescribing practices. Clinician focus groups will be planned to understand motivators for using certain fluids as opposed to others.

In terms of end-of-grant KT, the steering committee will be responsible for a manuscript summarizing the results which we will disseminate in a high impact peer-reviewed scientific journal. Dr. Rochwerg, Lamontagne and Alhazzani have significant experience as methodologists supporting societal clinical practice guidelines. Drs Rochwerg & Alhazzani were the methodologists for the 2016 SCCM Surviving Sepsis Campaign²¹ and will ensure the results of the FISSH trial get incorporated into future recommendations as a part of this guideline, especially given the dearth of current literature in this field. Social media is quickly gaining traction as a vehicle for knowledge translation and we will use avenues such as twitter (www.twitter.com) and online medical education blogs to increase awareness of the results.

FISSH Research Program Next Steps

Assuming this provincial trial proves feasible we plan to apply for further large-scale funding allowing for an international trial powered for 30-day mortality. This international trial will also include a built-in cost-effectiveness analysis component. The CCCTG has close ties with other national critical care trials group which will help facilitate this expansion (eg. Australian & New Zealand Intensive Care Group, Irish Critical Care Trials Group, Saudi Arabian Critical Care Trials Group, Scandinavian Society of Anaesthesia and Intensive Care).

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