**Assessment of the Concentration of Citrate during Haemofiltration**

**(ACCid HF)**

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**3. List of abbreviations**

*Abbreviation Term*

SCHHS Sunshine Coast Hospital and Health Service

NGH Nambour General Hospital

ICU Intensive Care Unit

USC University of the Sunshine Coast

HREC Human research and ethics committee

NEAF National ethics approval form

RCA Regional citrate anticoagulation

CRRT Continuous renal replacement therapy

CVVHF Continuous veno-venous haemofiltration

HF Haemofiltration

[citrate] Concentration of the citrate ion

i[Ca2+] Concentration of ionised calcium

κ Clearance (ml/min)**4. Synopsis**

Study title Assessment of the concentration of citrate during haemofiltration

Clinical phase Clinical

Trial design Single centre, prospective study

Rationale The primary aim of this study is to measure the plasma concentration of the citrate ion during CVVHF using CRA with a 15mmol/L HF fluid (NamSol).

The secondary aim is to investigate the performance of the haemofilters over time by quantifying citrate clearance across the haemofilter membrane.

Number of subjects As we are trying to establish a normally distributed range for [citrate] during CRA-CRRT, approximately 50 subjects will be required.

 In order to establish a zero point for the assay, a further 10 to 20 assays will be required. These assays will be performed on blood taken prior to the institution of CVVHF.

 In total, it is estimated that 50 patients will be enrolled.

Study duration The study will likely require a twelve to eighteen month recruitment and experimental phase followed by a two month analytical phase.

Endpoints The study will be closed when a total of 50 patients have been recruited.

Inclusion criteria Clinical requirement for CRA-CRRT in patients admitted to the NGH ICU.

Exclusion criteria Patients under the age of 18 years

 Patients who are pregnant

 Patients with advanced hepatic disease (Child’s C)

 Patients likely to die within 24 hours of admission to the ICU

 Known hypersensitivity to citrate compounds.

Centres Nambour General Hospital

Ethical approval Applications for ethical approval for the performance of the study will be submitted to the recommended HREC via the NEAF as appropriate and in accordance with the national guidelines.

**5. Administrative structure**

Study co-ordination and data collection will be based in the NGH ICU as a single centre. This centre will be responsible for all administrative aspects of the study including, HREC applications, protocol design, study performance, protocol training, data collection, organisation of investigator meetings as required, data analysis and ultimately, publication of results.

Specimen analysis will occur in batches at USC. Specimen logging, analysis, quality control and recording of results will be supervised on that campus.

Delivery of specimens will be co-ordinated between the two sites.

**6. Funding**

The current 15.0mmol/l solution (NamSol HF solution) is purchased as a standard bulk order item. Cost analyses have been undertaken by both the SCHHS and the USC. The study will be funded either by an external grant or from the NGH ICU research fund. The total cost is expected to be approximately AUD20,000.

**7. Background information**

Adult patients admitted to general ICUs with organ failures from any cause frequently require some form of renal support. In Australian ICUs, the most common method of supplying that support is through the use of one of the modalities of CRRT.

As a routine, the NGH ICU conducts CVVHF as a modality of CRRT using regional anticoagulation with a proprietary citrate based haemofiltration solution containing trisodium citrate in a concentration of 15.0mmo/L (NamSol).

Sodium citrate chelates ionised calcium in the plasma. Because calcium is an essential co-factor in the coagulation cascade, a state of reversible anticoagulation will exist when ionised calcium levels fall far enough (i[Ca2+] < 0.40 mmol/L). Ultimately the aim is to anticoagulate only the extracorporeal circuit (regional anticoagulation) and to ensure a normal state of coagulation in the intravascular compartment by infusing sufficient calcium, as calcium chloride, to restore normal levels of ionised calcium in the blood (1.15 < iCa2+ < 1.32 mmol/L).

The citrate containing anticoagulant solution is presented in 5.0 litre bags and infused directly into the afferent limb of the extracorporeal circuit at a rate of approximately 2.0 litres per hour. A proportion of the citrate is expectedly lost across the haemofilter membrane whilst the remainder enters the patients’ venous circulation and is ultimately metabolised mainly in the liver to carbon dioxide and water and to a lesser extent in striated muscle. Clearance of citrate from the vascular compartment is usually rapid in patients with normally perfused, healthy livers (κ ~ 700ml/min) but can vary markedly with the onset of critical illness (2).

Citrate is normally present in trivial amounts in the plasma as a by-product of normal metabolism with a mean plasma concentration in adults of approximately 0.10 mmol/L (95% CI 0.08, 0.18 mmol/L) (8,10). Whilst citrate is not toxic per se, significant accumulation can occur particularly in patients with limited reserves of clearance. It is therefore important to detect citrate accumulation in those patients with impaired metabolisation.

At present, plasma levels of citrate are not measured and toxicity is monitored by the use of a surrogate measure, the total to ionised calcium ratio. A recent study of 16 patients undergoing RCA CRRT found that although the correlation of total to ionised calcium ratio to plasma [citrate] was reasonable (R2 = 0.62), it could not be relied upon to detect all cases of hypercitrataemia (2).

In 2014, the NGH ICU used approximately 16000 litres of citrate containing HF fluid and whilst the safety profile is well documented, the actual plasma [citrate] was unknown. The establishment of an expected range will be essential if this treatment modality is to be expanded to either a wider patient population (eg: patients with hepatic disease) or to patients whose clearance of citrate may vary widely (eg: patients with severe sepsis). Ultimately, a rapid and accurate bedside assay may be developed.

In general, patients requiring CRRT, in whatever form, will need to be supported until their endogenous renal function recovers. This may take days in some cases to weeks to occur. It is anticipated that [citrate] will be tracked over time with levels taken, on average, twice a day.

Whilst in the ICU, all patients are intensively monitored looking for progress of their disease or recovery as well as early indicators of complications using standard protocols.

The NGH ICU conducts CRRT using RCA as a standard and preferred method and as a result, the study should proceed smoothly. The ICU has sufficient machines to treat four patients simultaneously and will have at least a two month stock of the haemofiltration solution.

**8. Study rationale**

The primary objective of the study is to document the plasma concentration of citrate ions during CRRT with a haemofiltration solution containing 15.0 mmol/L of sodium citrate as the sole extracorporeal circuit anticoagulant.

The secondary objective is to document the clearance of citrate through the haemofilter membrane.

This study has not been previously performed and is designed as a prospective trial to be conducted at the NGH ICU with measurement of [citrate] conducted separately at USC.

**9. Methodology**

*a) Research plan*: Acute kidney injury (AKI) affects up to 30% of ICU patients (1), with 5% of all patients requiring some form of CRRT. Of those patients requiring CRRT there is an associated high mortality rate secondary to their multiple organ failure (9).

CRRT involves an extracorporeal blood circuit through a haemofilter. This circuit requires anticoagulation to prevent filter clotting and subsequent treatment limitation. In Australian ICUs, systemic heparin is the commonest form of circuit anticoagulation but it is not without the risks of bleeding, heparin-induced thrombotic thrombocytopaenic syndrome and inadequate filter life (5,7). For these reasons, regional anticoagulation with a citrate containing renal substitution solution (haemofiltration fluid – HF fluid) has been widely accepted as a safe alternative option in patients requiring CRRT who are at risk of bleeding (4). Currently though, modalities of CRRT and formulations of citrate HF fluid vary with very real risks associated with administration errors (6).

At the NGH ICU, citrate HF has been used as our first line anticoagulant for patients requiring CRRT for more than 6 years. Furthermore, regional citrate anticoagulation is currently recommended as first line CRRT anticoagulation in the latest KDIGO guidelines (11). The citrate haemofiltration protocol used at the NGH ICU has the advantages of simplicity and safety by virtue of sole use of one HF fluid (Baxter NamSol 15.0mmol/l HF) for all patients requiring citrate based CRRT. In our experience, there have been no clinically significant adverse effects with the use of citrate HF fluid. We use a weight based prescription for CRRT as a routine (3).

In the last twelve months the NGH ICU has placed approximately 50 patients on RCA-CRRT with an average length of time on CRRT of approximately 6 days. At 2.0L/hr this translates to an annual use of HF fluid of about 14400 litres per year. Whilst we monitor for toxicity using the total to ionised calcium ratio, we do not know where the [citrate] lies within the therapeutic range. Quantifying [citrate] will permit finer titration of the CRRT prescription.

Patients who are enrolled in the study will have three blood samples taken each day at convenient times for the purposes of assaying both [citrate] and a standard panel of biochemistry ([Na+], [K+], [Mg2+], [Ca2+], [Cl-], [albumin], [phosphate], [urea] and [creatinine]). Part of each sample will also be analysed for pH, PCO2 and [lactate] using the ICU based ABL800 Flex acid-base analyser. A simultaneous sample of ultrafiltrate will also be collected. It will be analysed for [citrate], [urea] and [creatinine]. Because an infusion of calcium is used throughout the period of CRRT, it is further proposed to measure parathyroid hormone on enrolment, day 3 of CRRT and on cessation of CRRT.

CRRT will be performed using a weight based prescription and patients will be monitored for the end points of filter life, acid-base status, solute clearance and adverse events to ensure effective treatment and safety. The standard protocols for citrate based haemofiltration and calcium replacement will be used. Strict guidelines will be in place for treatment adjustments should there safety concerns arise.

*b) Screening*: Potentially eligible patients will be identified by their treating Intensivist. For all ICU inpatients, potential participants will be identified and the research team informed.

*c) Informed consent*: Those eligible will be offered the opportunity to participate in the research project. If, for reasons of illness acuity, a patient is unable to consent, the next of kin will be approached, or failing that, the Adult Guardian. The participant information sheet will be provided so the participant (or representative) may make an informed decision regarding study enrolment. Once agreement to participate occurs, the participant (or representative) will be asked to sign the study consent form. Once the consent form is signed, one copy is kept with the data and a second copy given to the patient.

*d) Randomisation*: Randomisation will not be necessary as this is a single arm study.

*e) Blinding*: Blinding is unnecessary as this is a single arm study.

*f) Procedures*: All procedures will be performed in accordance with existing standard CRRT protocols with the decision to commence CRRT based on biochemical and physiological parameters and at the discretion of the treating Intensivist. This is current practice.

(i) Vascular access: Using standard ICU protocols, a double lumen dialysis catheter (Vascath™) will be inserted under aseptic conditions and ultrasound control into one of the jugular veins, femoral veins or subclavian veins. Post-insertion radiography will confirm the position of the catheter and the absence of complications prior to use.

(ii) Haemofiltration: All patients in the study will receive NamSol (15.0mmol/L) at a predilution at a rate determined by a weight formula.

The blood pump will be set to a range of 150 to 250ml/min and all alarms will be activated.

Measurements of ionised calcium and serum magnesium concentrations will be performed according to existing standard protocols.

Haemofiltration will be prescribed in accordance with the standard ICU order form (see attached).

(iii) Cessation of CRRT: The decision to cease citrate CRRT will address the following points

1. A set of biochemical and physiological parameters that suggest that CRRT is no longer necessary. These parameters will be interpreted by the treating Intensivist as per standard care.
2. Where an alternative form of CRRT is deemed more suitable. Such as, in the case of:
	1. Evidence of citrate accumulation with the ratio of total to ionised calcium exceeding 2.5:1.
	2. Metabolic alkalosis with pH > 7.50 or SBE > 10.00mmol/l
	3. Inadequate solute clearance ([urea] persistently higher than 20.0mmol/l)
	4. A preference for intermittent haemodialysis where the patient may be leaving the ICU or is mobile during the day
	5. Recurrent filter clotting resulting in inadequate solute clearance.

(iv) Sample collection: Arterial blood will be collected using a standard intra-arterial catheter prior to and at intervals after the commencement of haemofiltration. Approximately 2ml of extra blood will be collected three times a day and all samples will be analysed using standard biochemical means, that is, a Beckman Coulter™ multianalyser for general serum samples and a Radiometer ABL800 Flex™ for acid-base samples. Samples of ultrafiltrate (~2ml) will be collected simultaneously. Blood samples for [citrate] assay will be spun and separated and all samples will be chilled to -80degC and transported to the USC for batch analysis.

Demographic data including age, sex, reason for admission and relevant co-morbidities will be collected by the research team. The progress of their renal function will be assessed by regular blood tests in accordance with standard ICU care.

**10. Data management and statistical analysis**

General demographic data, indices of severity of illness (APACHE II score), biochemical and acid-base data will be collected. After initial verification, all data will be subsequently reidentifiable.

Currently, the NGH ICU uses RCA CRRT to treat 40 to 50 patients per year with acute kidney failure, therefore a twelve month data collection time should suffice.

Statistical analysis will be performed using a propriety statistical package (STATA version 12.0). Data will be organised and trends reported using standard descriptive statistics (mean (SD), median (IRQ), proportions). More detailed inferential analysis will be done using regression techniques that take into account the linear and correlated nature of the data. All data will be analysed on an intention to treat basis.

The project will be managed locally by the principal investigator (CA). General data collection will be the responsibility of the ICU Clerical staff. Biochemical and acid-base data will be collected by the ICU Nursing staff. Consenting and enrolment will be the responsibility of the Consultant Intensivist on for the day. Oversight of the analytical component of the study will be managed at the USC.

Governance will be overseen by the local NGH Research Board.

Data will be stored on a secure local server. It is proposed to store the data for a maximum of five years after which it will be deleted.

All analyses will be performed at the end of the study and patients will be enrolled on an intention to treat basis.

**11. Human research ethics committee approvals**

An application requesting approval to conduct this study will be submitted to the HREC at the Royal Brisbane and Women’s Hospital. The content and format of the participant information statements and consent forms will also be submitted.

Each investigator will be responsible for the reporting of adverse events in relation to the performance of CVVHF in accordance with HREC guidelines. Any amendments to the study protocol and material will be notified to the HREC by the Principal Investigator.

All study records and documents will be securely stored for a minimum of 15 years from the end of the study or for a time period as required by the HREC.

*a) Withdrawal of consent*: At any time during the study the participant may withdraw consent. This is explained in the informed consent form and the patient information sheet and a withdrawal of consent form is available for signing. Withdrawal of consent will have no impact on quality of care and participants who continue to require CRRT will be no longer have blood sent for citrate assay.

*b) Adverse event reporting*: Adverse events will be reported to the HREC according to their guidelines.

*c) Protocol amendments*: Significant study protocol changes will have a written amendment request sent to the HREC for written approval. The approval letter will bear the signature of the HREC Chair and will refer to the protocol number, protocol title, amendment number and amendment date. The protocol amendment can only be implemented after HREC approval.

*d) Study termination*: The study may be terminated for any of the following reasons: study completion, failure of sufficient participant enrolment or at the discretion of the overseeing Research Board or Hospital board.

*e) Notification of study closure*: Within 3 months of either study completion or termination, the Principal Investigator will notify the HREC of that fact.

**12. Data quality assurance**

Data collection quality will be checked and assurance will be monitored by the trial co-ordinator.

*a) Principles*: The quality management principles will involve a patient focus, demonstration of leadership on the part of the investigator(s), education of both participants and their relatives involved in the study and the use of a systematic and factual approach to decision making. Overall conduct of the study will be overseen by the local research Board with regular reports on conduct and progress from the investigators.

*b) Safety considerations*: As a routine, all patients receiving CRRT are closely monitored with policies aimed at prevention of adverse events in place. If events occur, mechanisms currently exist to minimise the impact on patient safety and also to audit, report and investigate so as to educate staff and prevent recurrence. At any time, the CVVHF regime may be stopped at the discretion of the treating Intensivist. All morbidity and mortality is investigated by both local and hospital-wide committees.

*c) Follow up*: Patients enrolled in the study will be followed up in the wards after discharge from the ICU and also in the outpatients department after hospital discharge as advised by the treating Intensivist. At any time during or after completion of the project, they or their relatives will have access to a Consultant Intensivist to answer their questions. This is current standard practice.

*d) Records retention*: As previously stated, the Principle Investigator will retain and preserve one copy of all data generated in the course of the study for a period of 15 years following study closure.

**13. Publication and presentation**

It is proposed to publish the results in the peer-reviewed scientific literature with appropriate acknowledgement of all investigators. Similarly, it is proposed to present the results at appropriate postgraduate/scientific meetings.

Publication or presentation of the results may see repeated citrate assay form a normal part of the conduct of RCA CRRT in other institutes.

**14. References** (listed alphabetically by primary author)

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Clin Chim Acta 24: 335-40, 1969

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**15. Attachments**

Informed consent form

Next of Kin (Proxy) consent form

NGH ICU Citrate CVVHF protocol

Results sheet