**Base excess and renal substitution solution study**

**(BEaRSS Study)**

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**3. Signatures**

I have read and approve this protocol.

I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

*Principal investigator Signature Date*

Dr C M Anstey

*Co-investigators Signature Date*

Dr V Campbell

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**4. List of abbreviations**

*Abbreviation Term*

SCHSD Sunshine Coast Health Services District

NGH Nambour General Hospital

ICU Intensive Care Unit

RBWH Royal Brisbane and Women’s Hospital

HREC Human research and ethics committee

NEAF National ethics approval form

CRRT Continuous renal replacement therapy

CVVHF Continuous veno-venous haemofiltration

HF Haemofiltration

SBE Standard base excess

**5. Synopsis**

Study title Base excess and renal substitution solution study

Clinical phase Clinical

Trial design Single centre, prospective, randomised control study

Rationale The primary aim of this study is to examine the association between the citrate concentration in HF and the resulting SBE after several days of CVVHF. The secondary aim is to examine the relationship between citrate concentration in HF and filter life.

We expect to confirm that performing CVVHF using a relatively high citrate concentration HF (18.0mmol/l) results in an elevation of SBE. We expect to show that using a lower citrate concentration HF (15.0mmol/l) results in much less elevation of SBE.

We also expect to show that use of the lower citrate concentration HF results in an acceptable filter life.

Number of subjects It is estimated that approximately 25 subjects will be required in each of the two arms of the study. This estimate is based on a level of significance of 5%, a power of 80%, a mean reduction of SBE from 10.0mmol/l to 5.0mmol/l each with a common standard deviation of 5.0mmol/l.

From a recent retrospective audit of filter life, we found that by using the original 14.0 mmol/l HF a mean filter life of 24 hours (SD 16 hours) resulted whereas by using the current 18.0mmol/l HF, the mean filter life was extended to 65 hours (SD18 hours). By enrolling 25 patients in each arm, sufficient power will result to demonstrate an increase in filter life beyond 24 hours.

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

Endpoints The study will be closed when a total of 50 patients have been recruited (25 in each group).

Inclusion criteria Clinical requirement for citrate CVVHF 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.

**6. 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.

**7. Funding**

The current 18.0mmol/l solution (Baxter HF solution) is purchased as a standard bulk order item. The new fluid will be produced under a contract manufacturing agreement between Baxter Healthcare and Queensland Health and it will be supplied at the same cost as the current fluid. Stock of the current fluid will be decreased to accommodate the new fluid, so the study will be cost neutral.

**8. 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 18.0mmo/l (Baxter Haemofiltration Solution Citrate 18mmol/l).

Based on previous observations, it was noted that with the used of an 18.0mmol/l citrate solution, the patients developed a significant metabolic alkalosis after about 2 to 3 days of continuous therapy. It is postulated that this is due to the relatively high sodium content of the HF and that this alkalosis may be eliminated by using a fluid with a significantly lower sodium, and therefore lower citrate, content.

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. Because of the severity of illness suffered by these patients, they will nearly always require respiratory support on a ventilator as well. The presence of a significant metabolic alkalosis will cause a compensatory carbon dioxide retention through hypoventilation, which may slow the weaning of patients from ventilatory support. This aspect of CRRT will also be investigated.

Whilst receiving all treatments, the 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 citrate haemofiltration 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 both the standard and experimental haemofiltration solutions.

**9. Study rationale**

The primary objective of the study is to investigate the effect on the acid-base status between patients receiving CRRT using a haemofiltration substitution solution with a citrate concentration of 15.0mmol/l and those receiving CRRT using a solution with a citrate concentration of 18.0mmol/l.

Secondary objectives are to compare the length of life of the extracorporeal circuit and the incidence of complications associated with CRRT.

This study has not been previously performed and is designed as a prospective, randomised controlled trial to be conducted at a single site – the Nambour General Hospital Intensive Care Unit.

**10. 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 (10).

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 (6,8). 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 (5). Currently though, modalities of CRRT and formulations of citrate HF fluid vary with very real risks associated with administration errors (7).

At the NGH ICU, citrate HF has been used as our first line anticoagulant for patients requiring CRRT for more than 3 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 is based on the protocol used by the Austin Hospital ICU and has the advantages of simplicity and safety by virtue of sole use of one HF fluid (Baxter 18.0mmol/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 and similarly, we have also noticed that a weight-based prescription for CRRT also provides adequate clearances (4).

Recently however, increases in the HF citrate concentration have resulted in unwanted metabolic effects after continued use (2,3,9). Specifically, metabolic alkalosis with a standard base excesses exceeding 10mmol/l has been noted on many occasions. The clinical effect is unknown, but ventilatory wean time may be lengthened through a process of compensatory hypercarbia secondary to hypoventilation. Our hypothesis is that downward adjustment of the citrate concentration may result in better acid-base balance.

Prior to using the 18.0mmol/l concentration Baxter supplied an HF citrate solution containing 14.0mmol/l which we used successfully in the ICU for approximately 12 months. Due to an export arrangement this product is no longer available in Australia. As a result, we have approached the manufacturer (Baxter Healthcare) who have agreed to manufacture a renal replacement solution containing 15.0mmol/l of available citrate. We then propose to conduct a single centre, prospective, randomised study to compare acid-base status and filter life between the 15.0mmol/l and the 18.0mmol/l solutions. ICU patients who require haemofiltration will be randomised to receive either of the two solutions for the duration of their renal replacement therapy. Continuous veno-venous haemofiltration will be performed at a filtration rate of 2000ml/hour. 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 be safety concerns.

We aim to show that filter life is equivalent between the two solutions and that acid-base balance can be safely managed.

*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. As there is clinical equipoise in fluid selection, that is, either fluid would be acceptable as standard care with 18.0mmol/l (Baxter) and 12.0mmol/l (Gambro) citrate solutions in use in most Australian ICUs, we hope to gain permission for deferred consent.

*d) Randomisation*: Randomisation will be achieved using a blocked design to ensure numerical balance between the two groups and the resulting master list will be held by a person not involved in the trial. The fluids will be covered and only be identified as ‘Fluid A’ or ‘Fluid B’. Sealed envelops containing information about which fluid to use will be held in a secure place and opened sequentially as each patient is enrolled. In case the code needs to be broken, the responsible person will be contacted.

*e) Blinding*: The 5 litre bags of HF fluid will be covered with an opaque bag whilst hanging and all staff associated with the care of the patient, including the investigators, will be unaware of which solution is in use. Initial covering of the bags, delivery to the bedside and disposal will be performed by staff not involved in the study.

*f) Procedures*: All procedures will be performed in accordance with existing standard CRRT protocols.

(i) Commencement of CRRT: The decision to commence CRRT will be based on biochemical and physiological parameters and at the discretion of the treating Intensivist. This is current practice.

(ii) 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.

(iii) Haemofiltration: Depending on the result of randomisation, the patients will either receive the standard 18.0mmol/l solution (control group) or the 15.0mmol/l solution (experimental group) as a predilution at a rate of 2000ml/hour. Details of the solution constituents are listed in the table below.

|  |  |  |
| --- | --- | --- |
| *Constituents* | *Standard Solution* | *Experimental Solution* |
| Sodium | 152.0 mmol/l | 143.0 mmol/l |
| Potassium | 1.0 mmol/l | 1.0 mmol/l |
| Chloride | 99.0 mmol/l | 99.0 mmol/l |
| Citrate | 18.0 mmol/l | 15.0 mmol/l |
| *Calculated parameters* |  |  |
| Strong Ion Difference | 54 meq/l | 45 meq/l |
| Osmolality | 270 mOsm/kg | 258 mOsm/kg |
| pH range | 5.0 – 6.5 | 5.0 – 7.5 |

The blood pump will be set to 150ml/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).

(iv) 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 2.1:1.
   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.

(v) Sample collection: Arterial blood will be collected using a standard intra-arterial catheter prior to and at intervals after the commencement of haemofiltration. No excess blood needs to be collected 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. 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.

**11. 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.

From previous observation, it is anticipated that using the low citrate fluid, a reduction in standard base excess from a mean of 10 mmol/l (SD 5 mmol/l) to a mean of 5 mmol/l (SD 5 mmol/l) after 3 days of CRRT could be expected. Using a level of significance of 5% with a power of 80% gives a rough estimate of 20 participants in each arm of the study. Allowing for a 20% drop-out rate, a total enrolment of 50 patients (25 in each group) should be sufficient.

Similar statistics apply to the secondary analysis of filter life. The statistical power required to demonstrate an improvement in the filter life from 24 hours (SD 16 hours) to in excess of 60 hours (SD 16 hours) will be more than adequately covered using 25 patients in each arm.

Currently, the NGH ICU uses citrate 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.

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.

**12. Human research ethics committee approvals**

An application requesting approval to conduct this study will be submitted to the HREC at RBWH. 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 treated using the standard HF solution.

*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.

**13. 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, either 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.

**14. 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 this style of CRRT successfully taken up by other institutes.

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

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Crit Care 14(S): 515, 2010

8. Oudemans-van Straaten HM, Kellum JA, Bellomo R. Clinical review: anticoagulation for continuous renal replacement therapy – heparin or citrate?

Crit Care 15(1): 202, 2011

9. Silverstein FJ, Oster JR, Perez GO, Materson BJ, Lopez RA, Al-Reshaid K. Metabolic alkalosis induced by regional citrate hemodialysis.

ASAAIO Trans 35(1): 22-5, 1989

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Curr Opin Crit Care 12(6): 538-43, 2006

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**16. Attachments**

Informed consent form

Next of Kin (Proxy) consent form

NGH ICU Citrate CVVHF protocol

Results sheet