Study protocol

Prevention of Contrast-Induced Nephropathy by Combined Induced Diuresis with EuvolEmic Fluid Resuscitation

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1. Introduction and Background Information

Contrast-induced nephropathy (CIN) is a common complication associated with diagnostic and interventional coronary procedures, and is defined as ≥ 25% rise or absolute rise of ≥ 0.5 mg/dl in serum creatinine over the baseline value. Incidence of CIN is inversely related to estimated glomerular filtration rate (eGFR). Chronic kidney disease (CKD) is defined as kidney damage or a decrease in kidney function that lasts for at least three months. An eGFR of 15-29 ml/min/1.73m² is indicative of stage IV CKD, and an eGFR of <15 ml/min/1.73m² is indicative of stage V CKD (renal failure). An eGFR <60 ml/min/1.73m² is the single most common risk factor for development of CIN, with additional risk factors including volume of contrast, type of contrast, hydration status, recent radiocontrast exposure, diabetes mellitus, peripheral vascular disease, hypotension or shock, use of intra-aortic balloon pump, anaemia and congestive heart failure(1). Though gadolinium, an alternative contrast agent used in radiocontrast procedures, is generally correlated with a lower incidence of CIN, it is unsuitable for coronary procedures at present and has been shown to produce systemic fibrosis in renal failure patients(2). Pre-hydration, post-procedure diuresis, use of sodium bicarbonate, fenoldopam, N-acetyl cysteine, aminophylline, theophylline, dopamine, ANP, prostaglandin – all have been used to prevent CIN with diverse results(1). Currently pre- and post-procedural hydration, in addition to sparing use of iso/low osmolar radiocontrast agents, is the crux to reduce the risk of CIN. However, there is no consensus on how to use, how much volume to use, when to use and how long to use hydration. There is also no consensus on whether to use hydration alone or in addition to diuretics. Currently pre-procedural hydration is under-utilised, especially in patients with heart failure, due to fear of fluid overload and pulmonary oedema. Studies have shown that furosemide-induced diuresis and matched hydration may be used effectively and safely in patients with CKD and other co-morbidities(3); however, this has yet to be shown in patients with stage IV and V patients, nor has it been demonstrated in an Australian population. The current research protocol describes a randomised control trial, where high-risk patients for CIN will be randomised to forced diuresis with matched hydration, and will be compared with the current gold standard of conventional hydration to prevent CIN in our northern suburban regions of South Australia.

1. Aims and Hypotheses

**Aim:**

* To identify a novel, effective method of reducing rates of CIN in patients with advanced stage III, IV or V chronic kidney disease who are undergoing a radiocontrast procedure at the Lyell McEwin Hospital.

**Hypotheses:**

* Patients undergoing peri-radiocontrast procedures with pharmacologically induced forced diuresis along with euvolemic (matched) hydration can reduce the incidence of contrast-induced nephropathy.
* Length of hospitalisation after radio-contrast procedures will be reduced compared to current standard of treatment.

1. Study Design

This is a prospective comparative study comparing the current gold standard of conventional hydration and a new experimental approach to reduce the incidence of CIN in patients with advanced stage III, IV or V chronic kidney disease. This is determined by an eGFR <40ml/min/1.73m².

**Power Calculation:**

A power calculation was conducted assuming a CIN rate of 20% in controls based on the following assumptions:

* Inclusion of approximately 50% of chronic kidney disease patients with a NSTEMI, with an anticipated CIN incidence of more than 25%;
* An anticipated CIN rate of approximately 15% in chronic kidney disease patients undergoing elective procedures;
* A CIN incidence of 5% in the FMH group (15% absolute and 75% relative reduction)

Therefore, by averaging 25% and 15% CIN rates, the overall rate of CIN is expected to be 20% in control patients. Using a two-sided chi-square test with a significance level of 0.05 and 80% statistical power, 75 subjects in each group (with a total sample size of 166) were required to demonstrate the expected difference in the incidence of CIN between groups accounting for a 10% loss during follow-up.

**Consent:**

Patients will be approached and recruited by a member of the study team. After the participant has read the Participant Information sheet and informed consent has been obtained, patients will be randomised to either the control or the experimental group on a 1:1 basis using a block random number generator.

**Inclusion Criteria:**

* All adult patients with advanced stage III, IV or V chronic kidney disease undergoing elective or urgent diagnostic or therapeutic radiocontrast procedures will be approached for consent
* All patients that have a serum creatinine level of more than 1.6 mg/dl (145mmol/L) and eGFR of < 40ml/min/1.73m², and/or Mehran’s risk score of 6-16 will be included

**Exclusion Criteria:**

* Patients with contrast allergy
* Hypersensitivity to furosemide
* Patient on maintenance haemodialysis or peritoneal dialysis
* Radiocontrast procedure conducted within 72 hours
* Contraindication or failure to pass urinary catheter
* Patients with fluctuating baseline serum creatinine measurements
* Patients with acute renal failure
* Patients requiring emergency angiography procedures (i.e. STEMI cases)

**Randomisation:**

* After obtaining informed consent, patients will be randomised to one of the groups on a 1:1 basis using a block random number generator.
* Randomisation will be done 12 hours prior to the proposed procedure, as this gives ample time to pre-hydrate the patients in the conventional treatment arm.
1. Methodology

Participants will be required to give signed informed consent prior to participating in the study. Informed consent and randomisation will occur at least 12 hours before the scheduled procedure to allow time for the hydration required in the control group.

**Experimental Group:**

This protocol will be started 90-120 minutes prior to the scheduled contrast procedure.

* Baseline serum creatinine will be measured 2-4 hours prior randomisation.
* An 18-20G intravenous (IV) cannula inserted into an antecubital vein.
* A Foley catheter will be inserted as per normal hospital practice.
* Participants will be given 250ml of normal saline over 30 minutes via IV.
* Patients will also be given 0.5mg/kg body weight of IV furosemide at conclusion of bolus dose of saline.
* Hourly urine output will be measured manually from the time intravenous furosemide is given.
* Exactly the same amount of normal saline will be given over the next hour to replace the urine output from the previous hour (euvolemic replacement).
* If the patient does not produce an output of >300ml per hour, a repeat dose of normal saline and furosemide will be given as above.
* Once urine output of >300ml per hour has been reached, the patient will be taken to the radiocontrast procedure, where an iso-osmolar radiocontrast agent will be used.
* After the procedure, hourly output must be calculated and matched with fluid replacement and this will continue for 12 hours.
* If the urine output falls below/fails to reach 150ml/hr, then a repeat dose of furosemide will be given in the first 4 hours
* 12 hours after the procedure, the replacement therapy will be ceased and the patient encouraged to drink orally. The catheter is removed 12 to 24 hours after the procedure, as per standard hospital procedure.
* Serum creatinine will be measured daily for at least three days following the procedure. If there is a rising trend of serum creatinine, then serum creatinine levels will be followed up until the value stabilises (levels up) or begins to fall. Concurrent serum sodium and potassium will also be tested to observe the effect of massive fluid therapy and diuresis.

**Control Group:**

This protocol begins 12 hours prior to the scheduled contrast procedure.

* Baseline serum creatinine will be measured 2-4 hours prior to randomisation.
* An 18-20G IV cannula inserted into an antecubital vein.
* Patients will be given 1-2 mm/kg body weight of normal saline per hour, starting 12 hours prior to the procedure, continuing during the procedure and finishing 12 hours post-procedure.
* In the case of significant heart failure, the rate of fluid therapy will be tailored to 0.5ml/kg/hr to avoid pulmonary oedema or significant fluid overload.
* Serum creatinine will be measured daily for at least three days following the procedure. If there is a rising trend of serum creatinine, then levels will continue to be tested until the value stabilises or begins to fall. Concurrent serum sodium and potassium will also be taken to as per the experimental group.

All patients in both arms of the study will be observed either in the hospital bed or in virtual hospital bed by hospital-at-home, depending upon the rate of rise or fall in serum creatinine post-procedure, until they are out of the window of risk of CIN, or if they need further interventions or treatment. The length of hospitalisation will also be observed. Every patient will be followed up for safety, as per usual hospital procedure. Patients will also be followed up 6 months post-procedure, to determine their serum creatinine levels and to observe their longer-term outcomes.

1. Safety Considerations

The safety of all participants is of upmost importance. Participants will be asked to inform their treating doctor or nurse if they experience any serious discomfort during any stage of the procedure, and any adverse events will be reported according to usual hospital practice and ethical requirements. There are no additional risks for the patients associated with this study apart from the usual risks associated with angiographic procedures, including usual risk of CIN in these high-risk patients.

1. Data Management and Statistical Analysis
	1. **Data Management**

Data for this study will be stored of password-protected computers within password-encrypted files. The data will be collected directly from the patient or medical notes, where applicable. This project will also use an Excel spreadsheet to store patient information and data. A paper-based case report form will also be used and stored in locked filing cabinets in a secure research office. Patient information will be de-identified and allocated a non-identifiable study identification number. The data will be retained for a maximum of 15 years. Only the study investigators will have access to the study data. The study coordinator is responsible for managing the data.

* 1. **Statistical Analysis**

Statistical analysis will be performed using R software. To address the first hypothesis (categorical variables), a logistic regression and/or log binomial analysis will be performed. In addressing the second hypothesis (continuous variables), a linear regression analysis will be conducted. CIN is defined as ≥ 25% rise or absolute rise of ≥ 0.5 mg/dl in serum creatinine over the baseline value.

In terms of measurement of uncertainty (MU), the most recent calculation showed that U=4.5% at a creatinine level of 470 and U=6.1% at a creatinine level of 75. The published goal for total error for creatinine is <8.9%. This will be taken into account when performing data analysis.

In the analysis of secondary outcomes, account will be made for potential bias in outcomes, such as length of hospitalization.

1. Expected Outcomes

The current study is expected to provide rationale for adopting a novel method of forced diuresis and euvolemic hydration to reduce incidence of CIN in patients with advanced stage III, IV and V chronic kidney disease undergoing radiocontrast procedures. This study will compare the experimental method with the current gold standard treatment in an attempt to directly observe patient outcomes and incidences of CIN in the relevant patient population at the Lyell McEwin Hospital. It is also expected that the novel technique will improve patient outcomes and reduce length of stay in hospital.

1. Dissemination of Results and Publication Policy
	1. **Patient-Specific Results**

Patients will be informed of their clinical state and outcomes as per usual hospital operating procedure. There is unlikely to be any patient-specific results generated in this study, and as such, data pertaining to this project will not be reported to any patient.

* 1. **Publication of Results**

Following analyses of the data, the results of the studies in this research proposal will be presented to the study investigators. The findings will then be presented to various groups at the Lyell McEwin Hospital, the University of Adelaide, and may be submitted for publication. Any publications resulting from this study must be first approved by the Divisional Director of the Lyell McEwin Hospital. The principal and associate investigators, as well as any other persons who make significant contributions to the research, will be acknowledged where appropriate. The Lyell McEwin Hospital and the University of Adelaide jointly own the data.

1. Duration of the Project

The entire project is expected to take approximately 24 months. Initial participant recruitment and data collection is expected to take a maximum of 18 months, including 6-month follow-up visits. Another 6 months are allowed for data clean-up, analysis and generation of results for publication.

1. Problems Anticipated

Problems that may influence the successful completion of the project within the timeframe indicated, as well as possible solutions to these potential issues, are detailed below:

* Slow recruitment of participants
	+ Every effort will be made to ensure good communication is maintained between investigators and study coordinators so that every suitable participant is considered for recruitment.
* Significant variability in results
	+ The study is designed in such a way as to minimise random and systematic errors.
	+ Patients are randomised to one of the two groups using block randomisation.
1. Project Management

This is an investigator led randomised control trial, and will be managed by the principal and associate study investigators.

Study Investigators

* A/Prof Margaret Arstall is the Director of Cardiology Department at the Northern Adelaide Local Health Network (including Lyell McEwin Hospital and Modbury Hospital). She is a principal investigator on the proposed project.
* Dr Purendra Pati is a consultant interventional cardiologist at the Lyell McEwin Hospital. He is a principal investigator on the proposed project. He developed the research proposal in collaboration with the other investigators. Dr Pati is responsible for patient recruitment, data management, and analysis and presentation of the results.
* Emily Aldridge is the contact person for this study. She developed the research proposal in collaboration with the other investigators. She is responsible for ethics, data management, and analysis of the results.
* Dr Nitesh Rao is a renal physician at the Lyell McEwin Hospital. He is an associate investigator on this project. Dr Rao will be responsible for patient assessment.
* Dr Augustine Mugwagwa is a cardiology registrar at the Lyell McEwin Hospital. He is an associate investigator on this project. Dr Mugwagwa is responsible for patient recruitment, and analysis and presentation of the results.
1. Ethical Considerations

This research proposal will be conducted in accordance with the National Statement on Ethical Conduct in Human Research 2007. Approval is sought from the local Human Research Ethics Committee (TQEH/LMH/MH).

Participants whose primary language is not English, those in dependent or unequal relationships, Aboriginal or Torres Strait Islander peoples, or those involved in illegal activity may be coincidentally recruited into this study. Any concerns that arise will be addressed and the participant/s may be withdrawn or excluded from the study if necessary.

All participants have the right to withdraw from the study at any time without fear of jeopardising current or future medical treatment. It is important to note that withdrawal from the study once treatment has started may not alter the treatment course, however the particular patient’s information will be excluded from the study and no additional tests outside those necessary for clinical practice will be performed.

1. references

**1.** Sudarsky D, Nikolsky E. Contrast-induced nephropathy in interventional cardiology. Int J Nephrol Renovasc Dis2011; 4:85-99

**2.** Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant2006; 21:1104-1108

**3.** Marenzi G, Ferrari C, Marana I, Assanelli E, De Metrio M, Teruzzi G, Veglia F, Fabbiocchi F, Montorsi P, Bartorelli AL. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. JACC Cardiovasc Interv2012; 5:90-97