Neutrophil Gelatinase-Associated Lipocalin as an Early Marker of Contrast Nephropathy in Patients with Mild to Moderate Kidney Dysfunction

A. STATEMENT OF STUDY PURPOSE AND RATIONALE

Iodinated radiocontrast is administered frequently in the inpatient and outpatient settings, most commonly for procedures such as coronary angiography, percutaneous coronary interventions (PCI), and computed tomography (CT) scans. A serious complication of administering iodinated radiocontrast is a form of acute kidney injury (AKI) known as contrast-induced nephropathy (CIN). CIN is the third most common cause of AKI in hospitalized patients, thought to be responsible for up to 11% of all inpatient AKI (1). It is typically defined as renal impairment (increase in serum creatinine of > 0.5mg/dl or > 25%) occurring within 72 hours after contrast administration (2). Risk factors for CIN development include patient factors (age, presence of diabetes, CKD, or CHF), procedure-related factors (contrast volume administered, presence of intra-aortic balloon pump), and hemodynamic factors (hypotension, dehydration) (3-5). Multiple studies have shown CIN to be independently associated with greater mortality, increased length of hospital stay, and higher hospital costs (2). Because of its prevalence and association with excess morbidity and mortality, CIN has been a target of numerous prevention strategies such as intravenous hydration and N-acetylcysteine.

A major limitation of the literature is that most studies investigating CIN incidence, risk factors for its development, and methods for its prevention have been conducted in the setting of intra-arterial contrast administration (e.g., coronary angiography and PCI). Despite this, much of the data has been extrapolated and applied to patients receiving intravenous contrast for CT scans (6). It is currently unclear the extent to which these extrapolations are valid, given differences in patient populations, contrast volume administered, and intra-procedural complications between the two settings. The widespread and increasing use of contrast-enhanced CT—indeed, 90% of contrast media are used for CT scanning (7)—warrants more studies focusing specifically on CIN after intravenous contrast.

The diagnosis of CIN depends on serum creatinine (SCr), an imperfect marker of renal function for two main reasons: first, it is affected by several non-renal factors such as age, muscle mass, nutritional and hydration status, comorbid conditions, and medication use. Second, it accumulates slowly, making it of little use in non-steady state situations such as AKI (8,9). Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has recently emerged as a sensitive, specific, and early marker of AKI. Levels of uNGAL rise within 2 hours of injury (10, 11), rise in proportion to the extent of injury (10,12), and are NOT elevated in states of prerenal azotemia or stable CKD (13). Three studies have shown that uNGAL may an early biomarker of CIN occurring after coronary angiography and PCI (14-16). No studies have looked at changes in uNGAL after receiving IV contrast.

We propose to evaluate the ability of urinary NGAL to predict CIN occurring as a result of IV contrast administration during CT scan. Our central hypothesis is that in patients with some degree of baseline renal insufficiency, a rise in urinary NGAL is an early marker of CIN. This would be clinically useful in that hemodynamics could be more closely monitored and optimized in these patients, as well as other nephrotoxic exposures (aminoglycosides, NSAIDs, contrast etc.) avoided.

B. DESCRIPTION OF STUDY DESIGN AND STATISTICAL ANALYSIS

Study Aims:

1. To assess whether post-CT urinary NGAL is an early marker of acute kidney injury (AKI) due to intravenous contrast administration.

Study design:
Prospective cohort study of 600 in-patients with stable, mild-moderate chronic kidney disease undergoing contrast-enhanced CT scan. Using t-tests, we will compare the mean post-CT and delta (post-CT minus pre-CT) uNGAL levels in cases (those who develop CIN) vs. controls (those without CIN). Assuming a CIN incidence of 5%, our study should yield approximately 30 cases of CIN. This will allow us to determine an effect (i.e., mean difference in urinary NGAL between CIN cases vs. non-cases) of roughly one standard deviation with 80% power, assuming a p-value of 0.05.

Primary endpoint:
Occurrence of CIN, as defined by a greater than or equal to 0.5mg/dl rise in serum creatinine within 72 hours after contrast administration.

Variables to be collected:
1. Demographic
    - Age
    - Gender
    - Race
2. Co-morbidities
    - Diabetes mellitus
    - Congestive Heart Failure
    - Cancer
    - Cirrhosis
3. CT scan characteristics
    - Body part(s) imaged
    - Volume of contrast administered
    - Type of contrast administered (i.e., low vs. isoosmolar contrast)
4. Type of CIN prophylaxis administered, if any (e.g., N-acetylcysteine, IV fluids)
5. Kidney function
    - Baseline serum creatinine and estimated glomerular filtration rate (eGFR)
    - Serum creatinine and eGFR within 48 hours prior to contrast administration
    - Serum creatinine values within 72 hours after contrast administration
6. Urinary NGAL measurements
    - Within 24 hours prior to contrast administration
    - Within 4-12 hours after contrast administration

C. DESCRIPTION OF STUDY PROCEDURES:
A study coordinator will collect a sample of urine within 24 hours prior to CT scan, which will represent the pre-contrast uNGAL level. After the CT scan is performed, a study coordinator will return to the patient within 4-12 hours to collect another urine sample (representing the post-contrast uNGAL level). We will not employ the use of catheters to obtain urine unless they are already in place. We will also not administer intravenous or oral fluids for the sole purpose of obtaining urine. Serum creatinine measurements will be as per the primary team; operating under the assumption that most in-patients have daily monitoring of basic metabolic panel, we will not mandate any additional blood draws for this study.

D. STUDY DRUGS:

None

E. MEDICAL DEVICES:
None

F. STUDY QUESTIONNAIRES:
None

G. DESCRIPTION OF STUDY SUBJECTS:
Inclusion Criteria:

1. Adults age 18 and older undergoing contrast-enhanced CT
2. Pre-CT scan eGFR, calculated from serum creatinine obtained within 48 hours prior to contrast administration, of less than 90.
3. Baseline eGFR (determined from prior WebCIS data containing at least three serum creatinine measurements) that varies from pre-CT scan eGFR by no more than ten percent.

Exclusion Criteria:

1. Inability to provide informed consent
2. Patients who are in an ICU within 48 hours of CT scan
3. Patients who have end stage renal disease on chronic hemodialysis
4. Administration of the following drugs within 48 hours prior to or after contrast:
   • Aminoglycosides
   • Amphotericin B
   • Nephrotoxic chemotherapeutic agents (platinum-based agents, methotrexate, ifosfamide)
   • Non-steroidal anti-inflammatory drugs (NSAIDs)
   • ACE-inhibitors
5. A documented episode of hypotension (MAP<60) within 48 hours prior to or after contrast administration
6. Less than two serum creatinine measurements within 72 hours after contrast administration

H. RECRUITMENT OF SUBJECTS
A study coordinator stationed in the radiology scheduling department will monitor incoming CT scan requisitions and determine, via information in the electronic medical record (WebCIS and Eclipsys), whether the referred patients meet inclusion criteria. A study coordinator will approach those patients meeting inclusion and lacking exclusion criteria, and informed consent for study participation will be obtained.

I. CONFIDENTIALITY OF STUDY DATA:
All patients' written records will be kept secure in a locked location on campus. Computerized records are kept on a secure, password-locked internet database.

J. POTENTIAL CONFLICT OF INTEREST:
None.

K. LOCATION OF STUDY:
Columbia University Medical Center

L. POTENTIAL RISKS:
Patients will be asked to provide two small samples of voided urine for the study protocol. We will not employ the use of catheters to obtain urine unless they are already in place. We will also not administer intravenous or oral fluids for the sole purpose of obtaining urine. As such, there are no potential risks to patients.

M. POTENTIAL BENEFITS:
Application of the urinary biomarker NGAL to the early diagnosis of CIN, a significant cause of acute kidney injury in hospitalized patients. Given the morbidity and mortality associated with AKI, early detection (via uNGAL obtained soon after contrast administration) would allow patients at risk to have more close hemodynamic monitoring and observation, as well as the early cancelling/avoidance of nephrotoxic medications.

N. ALTERNATIVE THERAPIES:
Not applicable.

O. COMPENSATION TO SUBJECTS:
None.

P. COSTS TO SUBJECTS:
None.

Q. MINORS AS RESEARCH SUBJECTS:
Minors are not included in the study.

R. RADIATION OR RADIOACTIVE SUBSTANCES:
Not applicable.

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