Prevention of Contrast-Induced Nephropathy with the Combination of Sodium Bicarbonate and N-Acetylcysteine: A Randomized Controlled Trial

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A. Study Purpose and Rationale

Following coronary angiography, approximately 14.5% of patients develop contrast induced nephropathy (CIN).[1] In addition, CIN accounts for more than 10% of hospital acquired renal failure. Not only is CIN associated with increased lengths of stay, but also with worsening of baseline renal function, and, rarely, progression to hemodialysis.[1-2] Most importantly, CIN is associated with increased short and long term mortality.[2] Several studies have shown that the risk factors for developing CIN include baseline renal impairment,[3] diabetes mellitus,[4] and larger contrast loads (as with coronary angiography).[5-6]

While the exact pathophysiology of CIN is not known, it is thought that iodinated radiographic contrast causes direct tubular toxicity via free radical formation (which is promoted by the acidic tubular environment),[7] and by tubular vasoconstriction leading to ischemic injury.[8] Based on these insights, many attempts have been made to prevent CIN. It is now well established that the use of low osmolarity, non-ionic contrast agents is associated with decreased risk of CIN.[9] In addition, good evidence supports the use of the free radical scavenger N-Acetylcysteine (NAC) for the prevention of CIN.[10-12] Perhaps most widely accepted, intravenous hydration is considered integral for the prevention of CIN. In this setting, normal saline is the most frequently used intravenous fluid as it was shown in one study to be more effective than half-normal saline.[13-14] Most recently, however, new evidence suggests that hydration with sodium bicarbonate is more effective for prevention of CIN than hydration with normal saline.[15]

This study is designed to determine if there is a role for sodium bicarbonate in addition to NAC in the prevention of CIN in patients with renal insufficiency undergoing coronary angiography.

B. Study Design and Statistical Analysis

This is a single-center, double-blinded, randomized, controlled trial of NAC and sodium bicarbonate vs. NAC and sodium chloride for the prevention of CIN in patients with baseline renal insufficiency undergoing elective coronary angiography. Subjects will be randomized to receive either NAC and NS or NAC and sodium bicarbonate. Both groups will receive four doses of NAC 600mg PO BID, first on the morning of the procedure and ending the night after the procedure. The study group will receive 154mEq/L sodium bicarbonate in 4.23% dextrose in H2O at a rate of 3 ml/kg/hr for one hour before the procedure and then at 1 ml/kg/hr during and for 6 hours after the procedure. The control group will receive 154mEq/L sodium chloride in 5% dextrose in H2O at a rate of 3 ml/kg/hr for one hour before the procedure and then at 1 ml/kg/hr during and for 6 hours after the procedure. The primary outcome will be incidence of CIN, defined as $\geq$25% increase in serum creatinine or absolute rise >0.5 mg/dl within 48hrs after administration of contrast. Secondary outcomes will be change in creatinine clearance, length of stay and need for dialysis.

Assuming an incidence rate for the primary outcome of approximately 5% in the control group (as estimated from previous studies) and an incidence rate of 1% in the intervention group (a decrease that would be considered clinically significant), the study will require 333 patients in each group to detect a difference with a power of 80% (alpha 0.05). The protocol will be an intention to treat analysis. The data will be analyzed by t-test for continuous variables (change in CrCl and length of stay) and by Chi-square test for categorical variables (incidence of CIN, requirement for dialysis).

C. Study Procedure

Subjects will be identified by physician assistants during the performance of routine intake history and physical examination and then evaluated for enrollment by the research coordinator. The research coordinator will then assess eligibility and obtain informed consent from those that agree to participate. On the day of the procedure, the research pharmacy will provide the appropriate blinded fluid (normal saline or sodium bicarbonate) which will be infused as detailed above. Serum creatinine will be measured on the morning of the procedure and then as an inpatient on the first morning after the procedure and as an outpatient on the second morning after the procedure. In the case of a patient who must remain in the hospital for any reason, blood will be drawn as an inpatient on the second day. All serum samples for each patient will be measured together on a single day to reduce assay variability. The higher of the two post-procedure measures over 48 hours will be used for calculations.

D. Study Drugs

Sodium bicarbonate infusion will be prepared (154mEq/L sodium bicarbonate in 4.23% dextrose in H2O) and provided in a blinded fashion by the research pharmacy. In addition, both groups will receive the free radical scavenger NAC. NAC is an approved drug for other indications, however it is widely used for this indication despite its lack of FDA approval. No adverse events have been reported in multiple previous trials of NAC for the prevention of CIN, however, the potential adverse reactions include: hypotension, rash, pruritis, diarrhea, nausea, bronchospasm, and anaphylaxis. These effects will be monitored for by daily examination and patient self-reporting.

E. Study Subjects

Patients aged 18 and older with renal insufficiency (baseline serum creatinine of at least 2.0 mg/dl within one week of the procedure) and presenting for elective coronary angiography will be considered for enrollment in the study. Exclusion criteria will include: acute renal failure (serum creatinine drop of $\geq$0.5 mg/dl at the time of study when compared to measurement 1-3 months earlier), dialysis dependence, emergency catheterization, use of iodinated contrast within the previous 30 days, decompensated CHF within 30 days or known EF<30%, known cirrhosis, and allergy to NAC.

F. Confidentiality of Study Subjects

Each patient will be assigned a unique study-specific code number. All patient data will be kept securely in a password protected database on the research coordinator's computer.

G. Potential Conflict of Interest

None of the investigators has any vested financial interest in the outcome of the study.

H. Location of the Study

The study will be conducted at Columbia University Medical Center. The study site will be the Department of Medicine, Divisions of Cardiology and Nephrology.

I. Potential Risks and Benefits

In previous studies of sodium bicarbonate infusion, there have been no reported events of hypokalemia, hypokalemia-induced cardiac arrhythmia, or fluid precipitated acute pulmonary edema. Thus, while these theoretical risks exist, the risk to individual patients is expected to be very low. In the case of any of these adverse events, the usual standard of care management would be implemented. The only potential benefit of participation is the possible decreased incidence of CIN in the intervention group.

J. Compensation and Costs to Subjects

Subjects will not receive compensation for participation. There will also be no costs incurred by subjects.

K. References

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