Optimal Prophylaxis for Contrast-Induced Nephropathy Associated with Percutaneous Coronary Interventions for the Treatment of Acute Coronary Syndromes

Michael L. Arcarese

A. Study Purpose and Rationale

Acute renal failure secondary to exposure to radio-contrast media is associated with a significant morbidity and mortality, accounting for approximately 10% of in-hospital cases.[1] Furthermore, observational trials have shown that the incidence of acute renal failure associated with percutaneous coronary interventions (PCI) ranges from 3-14%.[2, 3] However, patients undergoing PCI tend to be at a higher risk for contrast-induced nephropathy (CIN) compared to patients undergoing elective angiograms and computed tomographic (CT) scans. Furthermore, observational trials have suggested that despite the low incidence, the significance of acute renal failure associated with PCI is substantial, showing that acute renal failure carries an increased risk for in-hospital mortality (OR 10.8), long-term mortality, and acute myocardial infarction.[3]

It is postulated that radio-contrast media induces nephropathy through several mechanisms, including induction of free radical species that lead to renal medulla oxidant injury.[4] Currently, peri-procedural hydration with normal saline is utilized as prophylaxis against contrast-induced nephropathy.[5] A recent randomized trial has shown that sodium bicarbonate infusion is more effective in reducing the incidence of contrast nephropathy compared with normal saline, although patients with the need for emergent cardiac catheterization were excluded from the trial.[6] However, several clinical trials involving a variety of purported renoprotective agents have failed to show consistent efficacy in preventing radio-contrast induced nephropathy.[7]

Therefore, the goal of this randomized control trial will be to elucidate the optimal strategy for the prophylaxis of radio-contrast induced acute renal failure associated with acute percutaneous coronary interventions.

B. Study Design and Statistical Analysis

This is a prospective, double-blind placebo controlled multi-center trial. Subjects will be randomized with a permuted block scheme to one of three treatment strategies: placebo with infusion of isotonic sodium chloride (ISC) of 3 cc/kg bolus over one hour pre-PCI followed by 1 cc/kg per hour for six hours post-PCI, placebo with bicarbonate infusion of 3 cc/kg bolus over one hour pre-PCI followed by 1 cc/kg per hour for six hours post-PCI, or acetazolamide with sodium bicarbonate infusion. The primary outcome of acute contrast-induced renal failure is defined as a 25% increase in the serum creatinine from the baseline value after 48 hours post-PCI.

Assuming a 10% incidence of the primary outcome in the control group based on previous observational trials, the study will be powered to detect a 40% relative risk reduction in acute contrast-induced nephropathy between the bicarbonate infusion with acetazolamide group and normal saline with placebo group, and a 20% reduction between the bicarbonate infusion alone and normal saline infusion alone. Therefore, 770 subjects will be randomized to each therapy. Outcome data will be analyzed with SAS software using a two-tailed chi-square analysis for categorical variables with an alpha of 0.05 and power of 0.8. The protocol will be an intention to treat analysis.

Table I will identify differences between groups that may affect the primary outcome and will include variables such as age, gender, BMI, baseline GFR (determined by the Modification of Diet in Renal Disease Study group equation[8]) history of diabetes, history of hypertension, previous PCI, presence

of hypotension (SBP < 90), use of diuretics, and contrast load during PCI. Any differences between study groups will be statistically controlled for in the final analysis.

C. Study Procedure

Patients will be evaluated for enrollment for this trial by the research coordinator after the diagnosis of an acute coronary syndrome has been made by the emergency department attending physician, in conjunction with the cardiology fellow who will triage the patient to an acute PCI. When the decision to proceed to acute PCI is made, subjects will be assessed for inclusion and exclusion criteria, and an informed consent process will be undertaken by the research coordinator. The coordinator will then notify the research pharmacy, who will supply the study drugs to the cardiac catheterization lab, and the initial bolus infusion and placebo or acetazolamide will be given concurrently with preparation for cardiac cath. Baseline chemistries will be obtained in the emergency room and follow-up serum chemistries (including serum creatinine) will be obtained at baseline and on days 1 and 2 of the trial and will be analyzed together on day 2 of the trial to reduce assay variability. A urinalysis will also be done at baseline, day 1 and day 2 to evaluate the effectiveness of the alkalinization therapy. This data will be obtained and analyzed by independent and blinded nephrologists. An independent data safety monitory plan will be utilized to evaluate for adverse events secondary to the study therapy. (see risks and benefits)

D. Study Drugs

A research pharmacy prepared blinded solution of 154 mEQ/L sodium bicarbonate in 5% dextrose and water will be used in this study. Furthermore, the carbonic anhydrase inhibitor, acetazolamide, at a dose of 250 mg PO Q12 hrs will be given on the day of the PCI. Acetazolamide effectively inhibits approximately 85% of the bicarbonate resorptive capacity in the proximal convoluted tubule of the nephron and acts to alkalinize the urine within 30 minutes, with a maximal response at two hours. The duration of action is approximately 12 hours. A low risk of adverse events is expected from the experimental therapy. However, acetazolamide has the potential to induce induce renal stone formation, hypokalemia, drowsiness, and parasthesias.[9] These potential adverse events will be monitored by a daily analysis of serum chemistries by an independent consulting nephrologists and by patient self-reporting of symptoms.

E. Study Subjects

Subjects ages 30-65 who are admitted to several New York City hospitals for an acute percutaneous coronary intervention for an acute coronary syndrome (STEMI, NSTEMI, UA) will be enrolled in the trial. The definition of an acute coronary syndrome will follow standardized AHA guidelines.[10] Patients will be included if they have a stable baseline serum creatinine greater or equal to 1.1 mg/dl. Patients will be excluded if they if had prior contrast exposure 7 days prior to admission, PCI in the past 6 months, current dialysis, acute renal failure, cardiogenic shock defined as sustained SBP < 90, acute pulmonary edema defined with clinical and radiographic criteria, history of cirrhosis, allergy to contrast media, or refusal or inability to consent for the study protocol.

F. Confidentiality of Study Data

All patient data will be kept anonymous and confidential in a password protected lap-top computer utilized by the research coordinator. The primary investigators and the consulting nephrologists will be blinded to the treatment assignments.

G. Potential Conflict of Interest

The investigators have no proprietary interest in the therapy under investigation.

H. Potential Risks and Benefits

In prior studies involving a similar hydration regimen, subjects experienced a mean increase in their mean arterial pressure of 10 mmHG, although no subjects developed heart failure or acute pulmonary edema. Patients had a small 2.1 mEQ/L statistically significant increase in serum bicarbonate, however, they had a non-significant reduction in serum potassium levels compared to normal saline infusion.[6] Adverse events, such as development of pulmonary edema, hypokalemia-induced cardiac arrhythmia will be treated according to the current standards of care. It is expected that patients will have an extremely low increased risk of adverse events such as pulmonary edema, hypokalemia-induced cardiac arrhythmia, or hypertension above and beyond their baseline risk of these events as a result of their acute coronary syndrome. Furthermore, reduction of contrast-induced nephropathy will have substantial benefits on their in-hospital and long-term mortality.

I. Compensation to Subjects

Compensation will not be provided.

J. References

1. Birck, R, Krzossok, S, Markowetz F, et al. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *The Lancet*2003;362: 598-603

2. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997; 103: 368-375.

3. Rihal, CS, Textor SC, Grill dE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circ*. 2002; 105:2259-2264.

4. Katholi, RE, Woods T Jr, Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis*. 1998;32:64-71.

5. Solomon, R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;331:1416-1420.

6. Merten, GJ, Burgess, WP, Gray, LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate. *JAMA*. 2004;291:2328-2334.

7. Murphy SW, Barrett BJ, Parfrey PS. Contrast Nephropathy. *J Am Soc Nephro.l 2000*; 11:177-182.

8. Levey, AS, Bosch JP, Lewis JB, et al. The modification of diet in renal disease study group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999; 130: 461-470.

9. Katzung, Bertram, MD, Ph.D. Basic and Clinical Pharmacology. Lange Medical Books/McGraw-Hill; New York: 2001, pp250-251.

10. Cannon, C, Battler, A, Brindis, R, et al. American College of Cardiology Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes of Patients With Acute Coronary Syndromes. *J Am Coll Cardiol*. 2001; 38: 2114-2130.