

# Protocol Development for Preventing Contrast-Induced Nephropathy

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**ABSTRACT-----** *Contrast-induced nephropathy (CIN) is related to substantial economic and clinical consequences, including extended hospitalization, the necessity for dialysis, and an amplified risk of death. As radiographic diagnostic testing becomes commonplace, a significant concern among practitioners is the prevention of radiographic contrast-induced nephropathy. Radiographic contrast agents are used most often in tests such as coronary angiography, percutaneous coronary angioplasty, atherectomy, and stent placement, computer-aided tomography (CAT) scanning, and magnetic resonance imaging (MRI). 1 Administration of these contrast agents often cause acute changes in renal function ranging from an acute reduction of renal function to the transient need for hemodialysis.*

*Early studies assessing the renal effects of radiocontrast administration in dogs proved a reduction in renal perfusion lasting up to 20 hours after radiocontrast administration. 8 Although no randomized controlled trial (RCT) has studied the benefits of hydration alone, it appears reasonable that sufficient hydration may offset some of the presumed hemodynamic effects that could lead to contrast-induced nephropathy. Various preventative strategies have been studied with mixed results.*

*This paper constitutes reviewing current and old practices and developing a tentative simple protocol for prevention of Contrast induced nephropathy in nearby hospitals.*

**Keywords---** Nephropathy, hydration, radiographic contrast, dialysis, renal perfusion

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## 1. INTRODUCTION AND BACKGROUND

Contrast-induced nephropathy (CIN) is related to substantial economic and clinical consequences, including extended hospitalization, the necessity for dialysis, and an amplified risk of death. As radiographic diagnostic testing becomes commonplace, a significant concern among practitioners is the prevention of radiographic contrast-induced nephropathy. Radiographic contrast agents are used most often in tests such as coronary angiography, percutaneous coronary angioplasty, atherectomy, and stent placement, computer-aided tomography (CAT) scanning, and magnetic resonance imaging (MRI).<sup>1</sup> Administration of these contrast agents often cause acute changes in renal function ranging from an acute reduction of renal function to the transient need for hemodialysis. This occurs in certain patient populations that have a preexisting renal impairment particularly when the reduction is secondary to diabetic nephropathy. Other factors in considering the moderate to high-risk patient include renal insufficiency (creatinine greater than 1.5 mg/dl), renal surgery, proteinuria, and uncontrolled hypertension. This reduction in renal function can lead to substantial morbidity and mortality during hospitalization and has been reported to account for more than 10% of hospital-acquired renal failure.<sup>2,3</sup>

Contrast-induced nephropathy (CIN) is defined as acute renal failure occurring within 48 hours of exposure to IV contrast that is not readily attributable to other causes. The serum creatinine level begins to rise within 24 hours of administration of IV contrast. Within three to five days, this level will typically peak then return to baseline values within 10 to 14 days. Various intrinsic causes of nephrotoxicity include vasoconstriction, direct renal toxicity caused by oxygen free radicals, decreased prostaglandin and nitric oxide induced vasodilation, increased oxygen consumption, and ischemia secondary to increased interstitial pressure, increased urinary viscosity, and tubular obstruction. Extrinsic causes of nephrotoxicity can be attributed to decreased intravascular volume, diabetes, hypotension, hypertension, sepsis, additional nephrotoxic drugs, and dehydration.

Early studies assessing the renal effects of radiocontrast administration in dogs proved a reduction in renal perfusion lasting up to 20 hours after radiocontrast administration.<sup>8</sup> Although no randomized controlled trial (RCT) has studied the benefits of hydration alone, it appears reasonable that sufficient hydration may offset some of the presumed hemodynamic effects that could lead to contrast-induced nephropathy. Various preventative strategies have been studied with mixed results. Administration of adequate hydration appears to be the easiest method to provide a renal protective outcome. Patients at risk of developing contrast induced renal impairment have received 0.9% normal saline at 1 ml/kg/hr approximately 6-12 hours prior to the procedure with a continuous infusion for 12-24 hours after the study as compared to 0.45% sodium chloride. It was clearly found that 0.9% infusion was superior to the 0.45% normal saline group.<sup>4</sup> The disadvantages of the volume expansion are that it is not suitable for patients with cardiac failure and is of limited use in emergency-situations where fluid administration for hours prior to the study is impractical.<sup>5</sup> A study by Merten et al compared a one-hour pre-procedure hydration with normal saline versus sodium bicarbonate.<sup>3</sup> Rates of contrast-induced nephropathy were lower in the sodium bicarbonate group than the patients receiving sodium chloride. However, the final results of this study are in question since the study was terminated early with the differences occurring possibly by chance. It is currently recommended that a 6-12 hour intravenous hydration regimen prior to and after radiocontrast alone or in combination with the sodium bicarbonate infusion (Sodium Bicarbonate 150 mEq in 1000 ml D5W at 3.5 ml/kg/hr for one hour prior to contrast study followed by 1.2 ml/kg/hr for six hours after contrast study completion) should be first line in preventative management of CIN.

Another method involves the use of N-acetylcysteine for CIN prevention. N-acetylcysteine has been the most widely studied of all prophylaxis strategies, although the mechanism for its claimed nephroprotective action is unclear. N-acetylcysteine might act by scavenging oxygen free radicals<sup>9,10</sup> or by enhancing the vasodilatory effects of nitric oxide.<sup>11</sup> Looking to the results from 22 trials<sup>12-33</sup> (2918 participants) compared N-acetylcysteine with placebo. The results showed that relative risks for contrast-induced nephropathy ranged from 0.11 to 1.5 (median, 0.72). Eleven of 20 trials that reported contrast-induced nephropathy and 13 of 20 trials that conveyed a variation in SCr level as an outcome preferred N-acetylcysteine prophylaxis (results from 5 studies were statistically significant). Furthermore, the initial study on N-acetylcysteine and radiocontrast nephropathy reported a 89% absolute risk reduction with N-acetylcysteine.<sup>6</sup> Many studies occurred to replicate these results with subsequent meta-analyses to follow. It was then reported that a reduction in relative risk of 0.44-0.65 occurred in favor of N-acetylcysteine with a dose of 600 mg orally every 12 hours for 24 hours prior and post study when combined with IV hydration during a 24-hour peri-procedure period together with non-ionic, low-molecular weight contrast. However, all the meta-analyses acknowledged potential flaws of study heterogeneity and publication bias.<sup>7</sup> It is generally accepted that although N-acetylcysteine is well tolerated and inexpensive, it is still unclear whether it significantly reduces the risk of radiocontrast-induced nephropathy. Nevertheless, the use of N-acetylcysteine is commonly employed as an option for the prevention of CIN.

Based on these current opinions, a protocol dependent on patient specific parameters is proposed for use in a hospital. (See attached Appendix I)

## 2. PROPOSED PROTOCOL

In the neuroscience Intensive Care Unit, identifying at risk patients for contrast induced nephropathy prior to CT scan or MRI is typically a hit-or-miss process. Some patients are identified while others are considered retrospectively. A process was implemented for the prescribing of agents to prevent moderate to high-risk patients from developing a contrast-induced nephropathy. The clinical NICU pharmacist will assume the responsibility of identifying, prescribing (with approval from the staff Neuro-Intensivist), and ensuring that the at-risk patient receives the CIN prophylaxis at the proper timing prior to study. During the morning rounding period, the NICU pharmacist will identify any at risk patient who will be undergoing a radiologic study with contrast dye. The pharmacist will then complete the "Contrast Nephropathy Protocol Medication Order" sheet and place it in the patient's chart. To expedite the administration of the prescribed agent, the Critical Care Pharmacy will be phoned to send the appropriate agent to the unit as soon as possible.

To assess compliance of this protocol, a list of patients who underwent a radiocontrast imaging will be obtained from the department of radiology on a daily basis. This list will be reviewed to assess whether the appropriate patients were identified, prescribed, and received prophylactic treatment prior to study initiation. This data can be further analyzed to measure compliance of this protocol.

## 3. ENDPOINTS FOR PROTOCOL SUCCESS

- 1) Compliance in the identification of moderate to high-risk patients for the development of contrast-induced nephropathy.
- 2) Compliance in the prescribing of prophylactic agents for CIN.
- 3) Decrease incidence of Radiocontrast nephropathy as defined as a rise of 0.5 mg/dl or  $\geq 25\%$  increase in serum creatinine over 48 hours post-procedure.
- 4) Appropriate timing of administration of CIN prophylactic agent (s)

- 5) Decrease need for dialysis procedure.
- 6) Decrease length of hospitalization

#### 4. CONCLUSION

The discovery of novel therapies for the prevention of contrast-induced nephropathy has been hindered by an incomplete understanding of its pathophysiology. Experimental and preclinical studies must continue to be a priority for investigators operating in this field. Risk factors for contrast-induced nephropathy should be thoroughly identified and categorized into patient related and non-patient related factors, before any prophylactic treatment is initiated. Patient-related factors include, diabetes mellitus, age, congestive heart failure, low hematocrit, hypertension, and low ejection fraction. Non-patient related factors, are related to contrast properties such as high- osmolar contrast, ionic contrast, contrast viscosity and volume.<sup>34, 35</sup>

In summary, there is suggestive, but incomplete, evidence supporting the use of hydration as a prophylaxis measure for contrast-induced nephropathy. Questions persist about whether all patients benefit equally from this treatment, as well as the optimal type, route, volume, and timing of hydration administration.

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**Appendix I: CONTRAST NEPHROPATHY PROTOCOL MEDICATION ORDER**

DATE:	PATIENT NAME:
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**ASSESS PATIENT FOR CONTRAST NEPHROPATHY RISK FACTORS**

Serum creatinine  $\geq 1.5$  mg/dl, diabetes, volume depletion, concurrent use of the following medications: NSAIDS, ACE Inhibitors, Angiotensin Receptor Blocker, Diuretics

**HYDRATION CONTRAINDICATED:**

**(Volume overload or severe heart failure/LV dysfunction)**

- N-acetylcysteine 600 mg orally every 12 hours x 4 doses
  - Initiate 24 hours prior to study or as soon as possible

**HYDRATION INDICATED:**

**(Radiologic procedure will be performed within 6 hours)**

- N-acetylcysteine 600 mg orally every 12 hours x 4 doses
  - Initiate 24 hours prior to study or as soon as possible

**CHOOSE HYDRATION REGIMEN:**

- Sodium Chloride 0.9 % 500 ml infusion over -----hours (choose 1-6 hours) prior to contrast study followed by Sodium Chloride 0.9% 500 ml infusion over 2 hours after contrast study completion

**OR**

- Sodium Bicarbonate 150 mEq in 1000 ml D5W at 3.5 ml/kg/hr for one hour prior to contrast study followed by 1.2 ml/kg/hr for six hours after contrast study completion

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Prescribing Physician Signature: