Review

Contrast Nephropathy

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ABSTRACT

Contrast nephropathy will increase mortality up to 30% following angiographic procedures. Before performing such procedures a careful reassessment of the risk/benefit ratio should be performed. Mannitol and diuretics play no role in prevention. Hydration and correction of abnormal electrolyte levels should be done in all patients. Pre-treatment with acetylcysteine and theophylline is a well-accepted strategy and should always be utilized. If creatinine levels are above 2.5 to 3 mg/dl, fenoldopam may provide additional protection, particularly in diabetic patients. However, the role of fenoldopam is controversial. Prophylactic hemodialysis may prove to be an additional tool in the fight against this disease in selected patients.

INTRODUCTION

Contrast nephropathy is defined as a rise in the serum creatinine level of at least 0.5 mg/dl within 48 hours of contrast medium administration.¹ While this is the most accepted definition, other definitions are cited, such as an increase in serum creatinine of more than 25% of the baseline level within 48 hours of administration of the contrast agent.

The incidence of contrast nephropathy is variable and ranges from 5% to 50% in various series. The lower incidence is observed in patients with mild renal dysfunction. Patients with creatinine >1.3 mg/dl, dehydration, diabetes mellitus and the concomitant use of nephrotoxic medications will have a higher incidence. With a higher dose of the contrast medium, the frequency of toxicity will be higher. Serious nephrotoxicity requiring dialysis, however, is rare and occurs in <1% of patients. In the era of modern interventional cardiology, many patients require multiple angiographic procedures during their lifetime. Any worsening in kidney function will render the patient even more vulnerable to further deterioration with future procedures.

RECEIVED: APRIL 30, 2003

REVISED AND ACCEPTED: JUNE 25, 2003

REPRINT REQUESTS:

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KEYWORDS:

Contrast nephropathy; Angiography; Acetylcysteine

Various degrees of renal dysfunction are frequently encountered in patients undergoing coronary angiography and other diagnostic procedures that utilize various radiographic contrast agents. The association is not by chance alone, for some risk factors that contribute to coronary artery disease are also frequently implicated in renal vascular disease. Patients undergoing coronary angiography frequently have concomitant renal artery stenosis.² Mild renal insufficiency is one independent predictor of the presence of significant coronary artery disease.³ With the worsening of renal insufficiency in patients undergoing angiography, it is not surprising that such patients will have a poor prognosis. Hemmelgarn et al. followed 16,989 patients undergoing coronary angiography for 1 year.⁴ Those patients who were undergoing kidney dialysis had a mortality of 15%, patients with serum creatinine levels >2.3 mg/dl had a mortality of 30%, while a mortality of 4% was found in patients with a creatinine level <2.3 mg/dl. This poor prognosis was found in other studies as well.^{5,6} Such a clinical impact, coupled with the fact that patients with renal insufficiency are likely to require more than an angiographic procedure, urges clinicians to spare no effort to try to prevent or lessen contrast nephropathy. Mechanisms of contrast nephropathy, and various techniques and medications utilized to achieve such a goal will be discussed.

Contrast agents will lead to an increase in osmolality. These increases may reflexively cause vasoconstriction of the afferent arterioles and subsequently medullary ischemia. These effects may be caused by calcium channels and are mediated by adenosine release. The ischemia will likely cause damage to the kidney, and that damage is mediated by oxygen free radicals.⁷ It is also suggested that contrast agents may have a direct toxic effect on the kidney, which may also be mediated through the production of oxygen free radicals. Occasionally an atheroembolus may be dislodged into the renal arteries during invasive angiography procedures, leading to renal dysfunction indistinguishable from contrast nephropathy (figure 1).

PREVENTION OF CONTRAST NEPHROPATHY

The first step in the prevention of contrast nephropathy is the careful calculation of the risk/benefit ratio prior to performing the procedure. This is of importance in patients with higher serum creatinine levels, particularly when there is concomitant diabetes, as they are the patients with the highest risk for the disease.⁸ Patients need to be well hydrated. Isotonic hydration is superior to half normal saline.⁹ Patients also need to have normal electrolyte levels and since hypomagnesemia increases the incidence of contrast nephropathy, magnesium levels should be normalized as well.⁷ Although the new low osmolar contrast agents are not routinely used in all patients due to their exorbitant cost, they should be utilized in patients with higher serum creatinine levels.⁸

The most important variable of the angiographic procedure is to use as little dye as possible. To achieve this, if at all possible, avoid left ventriculography. Utilize either a biplane

Figure 1. Mechanisms of contrast-induced nephropathy. Asterisk and crosses show the site of action of various agents. (GFR = glomerulate filtration rate; *low osmolar agents, hydration; **fenoldopam [use not universally accepted]; Calcium channel blockers [use not universally accepted]; +theophylline; ++N-acetylcysteine)

or a rotational cineangiography.¹⁰ Forced diuresis with mannitol or loop diuretics is not recommended because both may increase the likelihood of nephrotoxicity.¹¹

Acetylcysteine

Acetylcysteine has been proven to be a very valuable tool in the prevention of contrast nephropathy. It acts as a scavenger of oxygen free radicals, increases the expression of nitric oxide synthase, which improves the blood supply, and has an antiapoptotic effect. All of these actions lead to amelioration of the renal effects of the dye.¹² Tepel et al. randomized 83 patients to receive adequate hydration and either placebo or acetylcysteine in a dose of 600 mg orally before and after performing computed tomography. The study revealed a significant effect in preventing contrast nephropathy in the acetylcysteine group.¹³ Since the Tepel et al. study, most,¹⁴⁻¹⁶ but not all¹⁷ other studies have confirmed their findings. The most recent of those studies was the paper by Kay et al. They conducted a prospective, randomized double-blind, placebo-controlled trial on 200 patients with mild to moderate renal dysfunction, undergoing coronary angiography. Serum creatinine clearance was lower in the acetylcysteine group ($P=0.006$). In addition, the acetylcysteine group had increased creatinine clearance from 44.8 ml/min to 58.9 ml/min 12 days after angiography ($P<0.001$).¹⁴ The following are the key points of these trials.

- The results of most published studies were consistent revealing an improvement in creatinine of about 0.4 mg/dl.
- The benefit of acetylcysteine is observed in patients, regardless of the original cause of the renal dysfunction.
- The benefit of acetylcysteine was observed in those patients with mild to moderate dysfunction, as well as patients with creatinine above 3.0 mg/dl.

- Acetylcysteine should be used in conjunction with the generally accepted guidelines of hydration and less dye use. When the amount of dye exceeded 140 ml per procedure, the benefit was no longer observed.
- Patients with a higher risk of developing the disease, such as diabetic patients, received the most benefit from acetylcysteine.

Combining these facts with the low-risk and very low cost of the drug, acetylcysteine should be routinely administered to all patients with renal dysfunction undergoing contrast agent administration. In order for its benefit to be established in patients with more severe forms of renal dysfunction, or those requiring large volumes of dye, a large scale controlled study with a larger number of patients needs to be conducted.¹⁸

Dopamine and Fenoldopam

In order to improve renal blood flow, low dose dopamine was studied in controlled trials. It was found to be ineffective or only marginally beneficial.^{19,20} Dopamine is a non-selective agent and is not strong enough to counteract the contrast-induced afferent arteriolar vasoconstriction.²¹

Fenoldopam mesylate, a dopamine A1 receptor agonist, blocks the reduction in renal plasma flow. In a randomized study by Tumlin et al., 45 patients with chronic renal insufficiency were randomized to fenoldopam or placebo.²² The fenoldopam group had higher renal plasma flow and less rise in creatinine. There was no significant difference between the two groups in the contrast-induced nephropathy. The results are not surprising in light of the low power of the study. The only real criticism of this study is that, on average, the placebo group received more contrast dye compared to the active drug group. A large trial recently presented, but not yet in print, challenged the findings of Tumlin et al. and failed to show a benefit.²³ Given the inconsistent benefits and the significant cost associated with the fenoldopam, it should not be utilized. Whether it will have a role in certain subgroups of patients or at different dosing schedules warrants further study. Similar to acetylcysteine the benefit was more marked in the patients with concomitant diabetes.

Theophylline

Huber et al. conducted a notable study to assess the role of theophylline in the prevention of contrast nephropathy.²⁴ One hundred patients with baseline creatinine of approximately 2 mg/dl were randomized to 200 mg theophylline or placebo. Patients received a relatively large volume of contrast (at least 100 ml per patient). Theophylline resulted in preservation of kidney function and significantly decreased the incidence of contrast nephropathy. Contrast nephropathy was 4% in the theophylline group and 16% in the control group ($P=0.046$).

The benefit is likely attributable to the antagonizing adenosine effect on the afferent arterioles causing vasodilation which will ameliorate ischemia. A small study by Abizaid et al. failed to show a benefit, which was most likely due to the low

power of the study.²⁵ Before the use of theophylline becomes a widely accepted practice, its benefit needs to be replicated in a large scale trial.

Nifedipine

It is known that calcium plays a role in the genesis of afferent arteriolar constriction. It is thus thought that a calcium channel blocker, nifedipine, may have a benefit in preventing contrast nephropathy. Controlled studies showed no benefit, and the drug should not be administered for this purpose.²⁶

Prophylactic hemodialysis

An innovative idea is to provide hemodialysis to patients with renal dysfunction following angiography. Most,²⁷⁻³⁰ but not all,³¹ of the preliminary studies are encouraging. The key to its success is to shorten the time between dye administration and dialysis. Since dye effects start to occur 20 minutes post-administration, success hinges on starting the dialysis within this period. The negative study started dialysis within 280 minutes. In positive studies, dialysis started within approximately one hour of angiography. A large-scale controlled study is needed before a final recommendation can be established.

CONCLUSION

Renal insufficiency presents a challenge in patients with acute coronary syndromes. It is a common finding, and patients who have worsening kidney function following angiographic procedures will have a poor prognosis.³²⁻³⁴ This article is an attempt to lessen the risk of contrast nephropathy, thus improving the patient outcomes. An algorithm that helps clinicians achieve this goal is depicted in figure 2.

Figure 2. Suggested algorithm to decrease the incidence of contrast nephropathy prophylactic dialysis. (+Its role is still controversial, and not yet defined; !!Not universally accepted).

ACKNOWLEDGMENTS

The authors wish to thank Marshfield Clinic Research Foundation for its support through the assistance of Linda Weis and Alice Stargardt in the preparation of this manuscript and Dr. Graig Eldred for his critique.

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