ELSEVIER

Cardiovascular Revascularization Medicine 6 (2005) 82–88

CARDIOVASCULAR REVASCULARIZATION MEDICINE

Contrast-induced nephropathy: a review

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Received 26 May 2005; received in revised form 25 July 2005; accepted 25 July 2005

Abstract Contrast-induced nephropathy (CIN) is one of the leading causes of renal impairment in the United States and the third cause of hospital-acquired renal failure. Reduction in the incidence of CIN can lead to a decrease in the morbidity, mortality, and length of hospital stay. Although prophylactic hydration has been promising in decreasing the occurrence of CIN, other efforts such as diuretics, calcium channel blockers, theophylline, aminophylline, atrial natriuretic peptide, dopamine, and fenoldopam have been disappointing. The preventive effect of *N*-acetylcysteine on CIN has not been consistent in the literature. In a recent clinical trial, bicarbonate infusion was more effective than hydration in the prevention of CIN. Mechanical devices are in development to perfuse renal arteries with protective drugs during contrast exposure or for removal of contrast from coronary sinus during coronary angiography. In this article, we have reviewed available data in regards to CIN.

Keywords: CIN; Prophylactic hydration; *N*-Acetylcysteine; Bicarbonate infusion

1. Introduction, incidence, and definition

Contrast-mediated imaging studies are an integral part of modern medical practice. Contrast agents are used in more than 10 million procedures annually in the United States. One of the most important complications of contrast agents is kidney toxicity [1–6]. Contrast-induced nephropathy (CIN) is one of the leading causes of renal impairment in the United States [7–10] and the third cause of hospital-acquired renal failure [11]. McCullough et al. [12] reported that CIN occurs in 14.5% of unselected patients undergoing coronary angiography. In another study involving 1144 patients, the incidence of contrast nephropathy in patients who underwent cardiac catheterization was approximately 0.7% and increased to 20% in patients with baseline creatinine between 1.5 and 2.0 mg/dl [13]. Patients with renal insufficiency have a higher risk of developing atherosclerosis and thus will be frequently referred for angiography [14]. As such, in patients with decreased renal function, cardiovascular diseases are accelerated due to various abnormalities in atherogenic factors [15].

The total incidence rate of CIN in another study was 29% [16]. On the other hand, Berg [2] estimated the chances of CIN in the general population undergoing coronary angiography to be less than 2%. However, it could be as high as 80% in patients with diabetes and underlying kidney disease [1,11,17–21].

The impact of diabetes and existing renal insufficiency on the incidence of CIN has been studied by Parfrey et al. [7]. In a prospective study of patients with diabetes, renal insufficiency, and diabetes plus renal insufficiency, they determined that diabetic patients with normal renal function and nondiabetic patients with renal insufficiency are not at

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doi:10.1016/j.carrev.2005.07.004

an increased risk of nephrotoxicity. However, the risk for diabetic patients with preexisting renal insufficiency was found to be higher than the control group (8.8% vs. 1.6%, respectively).

Reduction in the incidence of CIN can lead to a decrease in the morbidity, mortality (up to 36%) and length of hospital stay [6,8,12,13,22–26]. In a recent meta-analysis, the incidence of CIN ranged from 2% to 26% in patients receiving *N*-acetylcysteine (NAC) plus sodium chloride and 11–45% in those patients administered sodium chloride hydration alone [21]. Although the use of low-osmolar contrast agents decreased the incidence of CIN, there is still a chance of CIN [19,27–30].

Different trials have used diverse definitions for CIN. These include a serum creatinine increase of more than 0.5 mg/dl [1,26,31–33] or more than 25% of the baseline level [12,34–36] at 24 [37], 48 [1,31–33,35,36], 72 [38], 96 [35], or 120 h [12] after contrast exposure.

2. Mechanism of CIN

The exact mechanism of nephropathy by contrast agents is not fully understood. Contrast agents have direct toxic effects on renal tubular cells [39] and renal hemodynamics, leading to selective reduction of outer medullary blood flow [40–44]. Based on several studies, oxygen radicals play a major causative role as the primary physiological insult [45–50]. Infusion of radiographic contrast agents, with the attendant increases in osmotic load and viscosity, increases the hypoxemia of the renal medulla and increases renal free radical production through postischemic oxidative stress [51,52]. This is due to decreased tissue oxygen tension, which promotes mitochondrial generation of reactive oxygen species [53,54]. On the other hand, hyperosmolar stress triggers cellular generation of reactive oxygen species [55,56]. The main superoxide-producing reaction in human disease is the Haber–Weiss reaction [57], which is mostly active in an acidic environment.

$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^-$$

Cooper [58] proposed the inactivation of endothelium-derived nitric oxide by hydroxyl radical ($OH^{\bullet}$), which is generated by iron. Because iron catalyzes the formation of the hydroxyl radical, the toxic effects of reactive oxygen intermediates increase when iron is present. Partially saturated iron-binding proteins, such as transferrin and ferritin, are unable to catalyze $OH^{\bullet}$ formation in vitro. Mobilization of iron from these proteins is necessary for iron stimulation of $OH^{\bullet}$ formation [59]. Protein-bound iron is often unable to catalyze $OH^{\bullet}$ formation [60–62]. Ferritin is the main protein in the storage of iron [63], and reactive oxygen radicals mobilize iron from ferritin. Reduction of Fe^{3+} in the ferritin core to Fe^{2+} by superoxide is essential [64]. However, Leehey et al. [65] concluded that oxidative stress secondary to iron infusion was not associated with acute renal injury, and there was no effect of ferric gluconate on glomerular permeability (albuminuria and proteinuria) or tubular function (enzymuria). Administration of the antioxidant NAC at doses utilized in the study of Leehey at al. [65] did not affect plasma and urinary measurement of lipid peroxidation (as a marker of oxidative stress).

3. Prevention

Although prophylactic hydration has been promising in decreasing the occurrence of CIN, other efforts such as diuretics [26], calcium channel blockers [66], theophylline [67], aminophylline [68], atrial natriuretic peptide [69], dopamine [70], and fenoldopam [71,72] have been disappointing in decreasing the incidence of CIN [19,26,67,69,73–75].

Because contrast agents preferentially reduce flow to the outer medulla, attempts to prevent CIN with vasodilators that do not augment medullary blood flow could worsen tissue hypoxia and thereby increase the incidence of contrast nephropathy [76].

Dopamine partially restored flow to the inner and outer cortex but had no effect on blood flow to the outer medulla [77]. However, CIN might result from hyperosmolar stress in the renal medulla, which is oxygen-deficient [51].

3.1. Volume and type of contrast agent

Existing evidence indicates that among patients with preexisting chronic kidney disease, the incidence of contrast nephropathy is not impacted by the volume of contrast. In a recent study to evaluate the role of volume of contrast in the development of nephropathy, Tardos et al. [78] reviewed 931 cases of coronary angiography and found 117 patients who had preexisting kidney disease (creatinine clearance <60 ml/min). They compared 22 patients who fulfilled the criteria for nephropathy with those without nephropathy and found that the volume of contrast was similar in both groups.

Gadolinium-based media have been proposed as the feasible alternatives to iodinated contrast for use in patients considered at high risk for nephropathy [79–83]. Kaufman et al. [79] have successfully used gadopentetate dimeglumine as contrast agent during peripheral vascular interventions in two patients, with no subsequent nephropathy. Matchett et al. [80] used gadopentetate dimeglumine as contrast agent at digital subtraction angiography in one azotemic patient without complication. Rieger et al. [81] studied the effect of gadopentetate dimeglumine on renal function in 32 angiographic procedures among 29 patients with advanced renal insufficiency (59% diabetic). Only one patient who had undergone renal angioplasty and stenting developed worsening of renal function; this was attributed