ELSEVIER

Cardiovascular Revascularization Medicine 12 (2011) 90 – 93

CARDIOVASCULAR REVASCULARIZATION MEDICINE

Review

Angiotensin-converting enzyme inhibitors and their effects on contrast-induced nephropathy after cardiac catheterization or percutaneous coronary intervention☆

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Received 8 November 2009; received in revised form 5 January 2010; accepted 7 January 2010

Abstract Contrast-induced nephropathy (CIN) is associated with increased morbidity and mortality in patients undergoing diagnostic procedures and/or interventional procedures in the cardiac catheterization laboratory. Angiotensin-converting enzyme inhibitor (ACEI) use has been implicated both as increasing the risk of developing CIN and as a protective factor against developing CIN. Because many patients who are referred for cardiac catheterization have comorbidities for which ACEIs are utilized, the precise role of these medications in the pathogenesis of CIN needs to be clarified. There is evidence both for and against a renoprotective effect of ACEIs in the development of CIN. However, virtually all clinical studies are relatively small studies and most of them are retrospective. Because of the important role that ACEIs play in the chronic treatment of the cardiac patient, further studies are warranted to define the role of the ACEIs in CIN when exposure to contrast is needed in this group of patients. Because CIN is an independent risk factor for increased morbidity and mortality in the cardiac patient, all efforts to decrease its incidence should be pursued. At the present time there is no compelling evidence for starting or stopping ACEIs before cardiac catheterization/coronary angiography or coronary intervention.

Keywords: Contrast-induced nephropathy; Angiotensin-converting enzyme inhibitors; Cardiac catheterization; Coronary angiography; Percutaneous coronary intervention

Contrast induced nephropathy (CIN) is most commonly defined as either a >25% increase in serum creatinine from baseline or an absolute serum creatinine increase of 0.5 mg/dl [1] after contrast administration. It is an iatrogenic disorder that is most often seen 48 to 72 h post-intravenous contrast exposure and its mechanism is poorly understood. Postulated theories for CIN include direct toxicity, oxidative stress, ischemia secondary to vasoconstriction, and tubular obstruction [2]. CIN has been shown to increase the length of hospitalization, the likelihood of dialysis, and mortality [3]. It has been reported that patients who require dialysis secondary to CIN may have a 2-year mortality rate as high as 80% [4].

Risk factors that have been cited as increasing the risk of developing CIN include preexisting renal impairment (Cr clearance of <60 ml/min), diabetes, congestive heart failure, advanced age, anemia, high volume of contrast media used, and reduced intravascular volume [4,5]. Patients undergoing coronary angiography and especially percutaneous coronary intervention (PCI) are deemed at particularly high risk for developing CIN because they often have the aforementioned risk factors [6]. In a database created by Mehran et al. [6], over 8000 patients undergoing PCI were

☆ There is no financial relationship between any of the authors and the subject matter.

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1553-8389/10/$ – see front matter
doi:10.1016/j.carrev.2010.01.002

identified and used to create a risk score for the likelihood of developing CIN post-PCI. The risk score, calculated based on the sum of integer scores assigned to various known risk factors such as hypotension (5 points), intra-aortic balloon pump use (5 points), contrast volume (1 point per 100 ml), glomerular filtration rate (GFR), and others, was formulated to predict the risk for both CIN and dialysis. A low score (≤5), for instance, carried a risk of CIN of 7.5% and risk of dialysis of 0.04%, whereas a high score (≥16) carried a risk of CIN of 57.3% and risk of dialysis of 12.6%.

Because of the necessity of coronary angiography and PCI, extensive research on methods to decrease the incidence of CIN post-procedure has been conducted. The use of nonionic low osmolar contrast [7], intravascular hydration [8], acetylcysteine [9], prostaglandin E_1 [10], and withholding nephrotoxic medications are some of the therapies tried to reduce CIN post-PCI. There has been some question regarding the role of angiotensin-converting enzyme inhibitors (ACEIs) to the occurrence of CIN and whether they increase or decrease the risk of CIN after coronary angiography/cardiac catheterization and PCI (Table 1).

ACEIs play an integral role in the treatment of patients with heart disease. They are utilized in treatment protocols for myocardial infarction, hypertension, heart failure, and have been shown to decrease the progression of renal disease in diabetic patients [11]. ACEIs have an inhibitory effect in the renin–angiotensin–aldosterone system (RAAS) such that they inhibit the production of angiotensin II. Angiotensin II has several important roles including that of a potent vasoconstrictor, mediator of cardiac remodeling, and stimulator of vasopressin and aldosterone. Some studies have shown that stimulation of the RAAS may be an important contributor to CIN [12].

In vitro studies that examined the cellular mechanisms of cellular stress and apoptosis suggested a possible protective effect against CIN with the use of ACEIs. Xiong et al. [13] demonstrated this effect using irbesartan, a selective AT_1 receptor blocker (ARB) in an in vitro animal cell line. ARBs, much like ACEIs, act via a common pathway to inhibit cell signaling triggered by angiotensin II. The study utilized existing evidence that reactive oxygen species (ROS) are involved in the pathophysiology of CIN. Hypothesizing that ROS-mediated apoptosis in renal tubular cells is a major contributor to CIN, the authors demonstrated that irbesartan attenuated contrast-induced renal tubular cell apoptosis in a rat cell line (NRK-52E) by reducing oxidative stress and by modulating mRNA expression of proteins involved in apoptosis of the renal tubular cells. It is speculated that ACEIs may act protectively by a similar mechanism.

In a small in vivo study into the mechanisms of CIN, Russo et al. [14] looked at alterations in renal perfusion as a key player in the incidence of CIN in patients with chronic kidney disease. By measuring GFR and renal plasma flow at set intervals following contrast administration, they demonstrated a near immediate decline in GFR proportional to the osmolarity of the contrast media employed and showed evidence that this was related to a renal hypoperfusion that was independent of a patient's volume status. It was further demonstrated that a single dose of captopril or the calcium channel blocker nifedipine prior to exposure to contrast media could attenuate this decrease in GFR and renal plasma flow by 20% in patients with chronic kidney disease, thereby hypothetically reducing the incidence of CIN.

On a broader level and due to their intimate involvement with the RAAS, ACEIs have been hypothesized to decrease the incidence of CIN. One of the earliest clinical studies to demonstrate a decrease in CIN with ACEIs was conducted by Gupta et al. [15] in 1999. Gupta et al. [15] randomized 71 diabetic patients undergoing cardiac catheterization to captopril 25 mg tid for 3 days starting 1 h prior to procedure vs. no ACEI therapy. Their results showed that the captopril group had a reduced risk of developing CIN by 79% [15]. Gupta et al. [15] hypothesized that ACEIs have a protective effect by opposing the arteriolar vasoconstrictive effects of contrast media induced by the activation of the RAAS [15].

While Gupta et al. [15] demonstrated a decrease in CIN with ACEIs in diabetic patients, Dangas et al. [16] illustrated a protective effect in patients with chronic kidney disease. It was in a retrospective study of over 7000 patients undergoing percutaneous intervention that Dangas et al. [16] found that preprocedural ACE inhibition resulted in a lower risk of CIN in patients with chronic kidney disease

Table 1
Summary of the studies reviewed in this article

Study	*n*	Study description	Results	*P* value
Russo et al. (1995) [14]	14	Effect of captopril on decline in GFR in CKD patients exposed to IV contrast	Captopril (or nifedipine) reduced the incidence of renal hypoperfusion as measured by the decrease in GFR and renal plasma flow by 20%	<.05
Gupta et al. (1999) [15]	71	Captopril prevention of CIN in diabetic patients	ACEI group: 6% Control group: 29%	<.02
Toprak et al. (2003) [18]	80	Captopril prevention of CIN in patients with normal kidney function	ACEI group: 10.4% Control: 3.1%	.02
Cirit et al. (2006) [19]	230	Chronic ACEI users with mild-moderate renal impairment and the risk of developing CIN post-PCI	ACEI group: 15.6% Control group: 5.8%	.015
Rosenstock et al. (2008) [3]	283	The effect of ACEI withdrawal in patients with CKD and chronic ACEI users prior to PCI and the incidence of CIN	Chronic ACEI in continuation group: 6.2% Chronic ACEI in discontinuation group: 3.7% ACEI naïve group: 6.3%	.66

[odds ratio (OR) 0.61, 95% confidence interval (CI) 0.44–0.86, *P*=.005] but not in those with relatively normal renal function [16].

Despite the several groups providing evidence that supports ACEIs decreasing CIN, there are several studies that refute this claim. Hölscher et al. [17] sought to prospectively assess predictors of CIN and long-term outcomes of affected patients. Utilizing the data from the 412 patients studied in the Dialysis-Versus-Diuresis trial, post-procedural hemodialysis, left ventricular ejection fraction <35%, serum phosphate, and ACEI use were found to be independently associated with increased incidence of CIN. ACEI intake was associated with a sixfold increase in the incidence of CIN post-procedure (OR 6.16, 95% CI 2.01–18.93). Interestingly, ARBs did not exhibit a similar effect. However, the number of patients on ARBs was not large enough to show statistical significance.

Toprak et al. [18] showed that ACEIs increased the incidence of CIN in a study performed in 2003. Their study design was similar to that of Gupta et al. [15]. Toprak et al. [18] studied a population of 80 individuals with serum creatinine <2 mg/dl. Captopril was administered in 48 patients. It was given at 48, 8, and 1 h prior to procedure vs. the control group who received no ACEI therapy. The results showed that five patients (8.3%) on the ACEI therapy vs. one patient (3%) in the control group developed CIN (the difference was statistically significant with a *P* value of .02). This study concluded that ACEIs increase the likelihood of CIN post-PCI.

Both the Gupta et al. [15] and Toprak et al. [18] studies were limited in the size of the study population (79 and 81 patients, respectively). The study focused on patients with diabetes and patients with relative normal kidney function. Other factors such as hypertension, prior renal disease, volume of contrast given, congestive heart failure, etc., were not taken into consideration in these early studies. Furthermore, ACEIs were given acutely and the use of chronic ACEIs was not evaluated. The limitations of these studies were taken into consideration when Cirit et al. [19] performed a study evaluating chronic ACEI use as a risk factor for developing CIN. They hypothesized that CIN was likely due to the vasoconstrictive effects mediated by RAAS activation and that chronic ACEI use would attenuate this effect [19]. Cirit et al. [19] evaluated 230 patients with mild-moderate renal insufficiency (eGFR range of 31–88 ml/min with a mean of 51 ml/min) and randomized them into chronic ACEI users (taking any ACEIs for at least 2 months, *n*=109) and those not taking an ACEI (*n*=121). The study population was given intravenous saline prior to and post-procedure, while other renal protective agents (such as acetylcysteine) were not given. Low osmolar, nonionic contrast media was used, and diuretics and metformin were held prior to angiography. Both groups had similar eGFR and Cr prior to procedure. The study results showed that out of the 24 (10.6% of the study population) patients who developed CIN, 17 belonged to the ACEI group (15.6% of ACEI population) and 7 belonged to the control group (5.8% of control population) (*P*=.015) [19]. The study further evaluated ACEI subgroups; however, no statistical significance was found among the subgroups. In multivariate analysis, the risk factors for CIN included chronic ACEI [risk ratio (RR) 3.37; *P*=.028], multivessel coronary involvement (RR 6.24; *P*=.001), diabetes mellitus (RR 5.60; *P*=.006), hypoalbuminemia (RR 5.79; *P*=.005), GFR <40 ml/min (RR 4.84; *P*=.010), and congestive heart failure (3.36; *P*=.024) [19]. The variables they found that were not statistically significant risk factors included age, female gender, hypercholesterolemia, left ventricular ejection fraction, serum creatinine, contrast amount, inferior vena cava index, anemia, and hypertension [19]. They postulated that ACEI inhibition of the production of angiotensin II leads to a decrease in glomerular hydrostatic pressure and thus glomerular filtration [19,20]. The decrease in glomerular filtration combined with contrast media's detrimental effects in the kidneys likely results in the occurrence of CIN in this patient population.

The Cirit et al. [19] study touched upon the question of whether or not to hold ACEIs prior to contrast exposure in order to decrease the risk of CIN. This question was further addressed by Rosenstock et al. [3] when they performed one of the largest published randomized prospective trials on ACEIs and CIN. Their focus was on determining whether holding ACEIs prior to angiography causes a withdrawal effect and possibly increasing the incidence of CIN. The study enrolled 283 patients on chronic ACEI therapy (>2 months) with chronic kidney disease (GFR 15–60 ml/min per 1.73 m^2). They divided their study population into three groups: chronic ACEI users who continued ACEI therapy through the procedure (*n*=113), chronic ACEI users who discontinued ACEIs prior (withheld in the morning of the procedure and for 24 h post-procedure) to procedure (*n*=107), and ACEI naïve patients (*n*=63). Both groups were similar in most aspects except for the incidence of diabetes and hypertension, which was statistically significantly low in the ACEI naïve group. Patients were hydrated based on the institutions' policies, and medications such as diuretics and metformin were held prior to the procedure [3]. Acetylcysteine was used on a subgroup of patients, but no statistical significance in reduced occurrence of CIN was found in this subgroup compared to nonusers (*P*=.63) [3]. The authors found no statistically significant differences between the groups in the incidence of CIN: continuation group 6.2%, discontinuation group 3.7%, and naïve group 6.3% (*P*=.66). The authors cited limitations of their study to include measurement of creatinine values 24 h post-procedure (further measurements were at the discretion of the treating physician) and not comparing the various ACEI subgroups [3]. Rosenstock et al. [3] concluded that ACEIs do not increase the incidence of CIN. They recommended not withholding ACEIs prior to contrast exposure.

In conclusion, CIN is a known complication of iodinated contrast administration during coronary angiography/cardiac

catheterization and PCI. The mechanism(s) remain(s) unclear, but there are several identifiable risk factors that increase the likelihood of developing CIN post-contrast exposure. Patients who experience renal failure post-procedure have an increased mortality rate when compared to those who retain normal renal function [21]. Preventive measures such as intravenous hydration, acetylcysteine, use of low osmolar nonionic contrast, calcium channel blockers, dopamine, and fenoldapam have been used with variable success [2]. This review focused on the role of ACEIs in CIN. The data regarding ACEIs and CIN are conflicting. There have been studies that report a protective effect [15], studies that report a negative effect [18,19], and studies that report no effect [3]. Based on the data, there is no definite correlation between ACEIs and the occurrence of CIN post-contrast exposure in the cardiac catheterization laboratory. Even when evaluating specific subgroups, such as those with chronic kidney disease, the data are not consistent and a definitive correlation between ACEIs and CIN cannot be established. Thus, withholding ACEIs prior to catheterization does not probably decrease the incidence of CIN and is not recommended. By the same token, starting ACEIs before the procedure for the sole purpose of lowering the risk of CIN cannot be recommended based on the current evidence.

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