Shall We Stop or Continue Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Prior to Using Contrast Agents?

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There are conflicting results about using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) before administration of contrast media for imaging. It is well taken that many predisposing factors can be present to induce contrast-induced nephropathy (CIN). Nowadays, we are encountering increasing number of patients with CKD and diabetes mellitus, especially elderly with preexisting kidney failure, heart failure, and hypovolemia who may need any intervention such as coronary angiography or percutaneous procedures. Researchers continue attempts to find less toxic and advise using lower doses of these agents, but CIN is still the 3rd leading cause of hospital-acquired acute kidney injury, accounting for 12% of cases.[1] The incidence of CIN is usually less than 2% in patients who do not have any risk factor for CIN, but it can rise up to 50% or more in patients with multiple risk factors.[2] The incidence of CIN is over 20% in patients with renal insufficiency and over 10% in the elderly.[3,4]

Does the occurrence of CIN have any impact on patient's outcome? The answer is yes; these patients have much worse outcome than patients without CIN.[5] They have also other associated significant consequences, including prolonged hospitalization, indication for dialysis, and an increased risk of death.[6] Dangas and colleagues[7] showed that in-hospital outcome rates, such as death (6.3% versus 0.8%), cardiac death (4.0% versus 0.5%), coronary artery bypass grafting (5.8% versus 0.5%), major adverse cardiac events (9.3% versus 1.1%), were significantly higher in patients who developed CIN as compared with control patients ($P < .001$).

Angiotensin-converting enzyme inhibitors play an integral role in the treatment of patients with heart disease. They are utilized in treatment protocols for myocardial infarction, hypertension, and heart failure, and have been shown to decrease the progression of kidney disease in diabetic patients. Despite considering all risk factors and pointing to all the possible indicated procedures for prophylaxis and preventing CIN, still there are paradoxical conclusions about the role of the renin-angiotensin-aldosterone system RAAS in CIN and blocking angiotensin-II with an ACE inhibitor and or an ARB. There is evidence both for and against the renoprotective effect of ACE inhibitors and ARB in the development of CIN. Some studies pointed out that it was effective in the prevention of CIN,[8] while some concluded that it was a risk for the development of CIN.[9,10] The evidence can be explained based on the results of a few studies on the action of angiotensin II on sodium-depleted dogs, in which this depletion accentuates both the magnitude and duration of the vasoconstrictive phase of the renal blood flow response to injection of contrast medium and the blockade of the intrarenal RAAS shortens the duration of this response.[11] Activation of the RAAS could cause vasoconstriction of the efferent glomerular arteriole, while at the same time increasing the synthesis of vasodilator prostaglandins, resulting in almost stable or slightly increased intrarenal resistance. Inhibition of angiotensin II prevents vasoconstriction and generation of reactive oxygen species and increases the synthesis and bioactivity of nitric oxide.[12,13]

Meanwhile, recently investigators have found that transforming growth factor-β1 (TGF-β1) prevents from renal proximal tubule cell necrosis.[14] Angiotensin II can stimulate the formation of cytokines TGF-β1 and ACE inhibitor, preventing the protective effects of angiotensin II-mediated TGF-β1 in acute kidney injury as illustrated by a model of hydrogen peroxide-induced human proximal tubule cell necrosis where exogenously administered TGF-β1-induced tubular protection and neutralizing TGF-β1 antibody prevented the renal tubular cytoprotection.[14] It may be a possible role for the harmful effects of ACE inhibitors in CIN.

In this issue of the *Iranian Journal of Kidney Diseases*, Spatz and colleagues reported the incidence of CIN in 178 patients with chronic kidney disease stage 3 or 4 who underwent coronary angiography; 62 patients (35%) were on ACE inhibitors, 12 patients (7%) were on ARBs and 1 patient (1%) was on a combination of ACE inhibitors and ARBs. On day 2, 13% of patients had experienced acute kidney injury (AKI). The peak incidence of AKI was on day 3 at 19%. The odds ratio of AKI on day 5 was 0.73 (95% CI, 0.31 to 1.69) for ACE inhibitor and 0.46 (95% CI, 0.06 to 3.70) for ARB. Multivariable analysis revealed the findings to be independent of demographic variables, comorbidities, type of contrast medium, and the prophylactic strategies utilized.[15]

Some reports have implicated ACE inhibitors as nephrotoxic and exacerbating kidney failure with CIN, especially for patients with preexisting kidney function impairment, congestive heart failure, and the elderly.[16] Angiotensin-converting enzyme inhibitors can often cause a decrease in glomerular filtration rate (GFR) and can increase serum creatinine level, which may predispose to the development of CIN in patients taking ACE inhibitors. Toprak[16] performed a randomized controlled study on 80 patients with serum creatinine levels less than 2 mg/dL, who were assigned to captopril group (n = 48) and control group (n = 32). Five patients (10.4%) in the captopril group developed CIN, compared with only 1 patient (3.1%) in the control group (P = .02). The results showed that 5 patients (8.3%) on the ACE inhibitor therapy versus 1 patient (3%) in the control group developed CIN, and concluded that ACE inhibitors increased the likelihood of CIN after the procedure. Krusov´a and coworkers[17] reported that a combination of ACE inhibitors and furosemide was risky medication, which resulted in a significant decline in GFR and a rise in proteinuria in the subgroup of patients with diabetes mellitus and hypertension. Some published reviews on the subject have suggested holding these drugs for 24 hour prior to an angiography.[18] Cirit and colleagues performed a study evaluating chronic ACE inhibitors use as a risk factor for developing CIN. They evaluated 230 patients with mild to moderate renal insufficiency (estimated GFR range of 31 mL/min to 88 ml/min; mean, of 51 mL/min) and randomized them into chronic ACE inhibitor users (taking any ACE inhibitors for at least 2 months, n = 109) and those not taking an ACE inhibitor (n = 121). Both groups had similar estimated GFR and creatinine level prior to the procedure. The study results showed that out of the 24 (10.6% of the study population) patients who developed CIN, 17 belonged to the ACE inhibitor group (15.6% of ACE inhibitor population) and 7 belonged to the control group (5.8% of control population; P = .02).[19] The study further evaluated ACE inhibitor subgroups; however, no statistical significance was found among the subgroups. Moreover, angiotensin II injection aggravates CIN in rats. Conversely, in the presence of acute contrast-induced reduction of renal blood flow, blunting the vasoconstriction of efferent arteries by angiotensin II may have a deleterious effect on GFR by reducing the intraglomerular pressure. These opposite effects explain probably why the studies to date have been controversial on this issue.

Holscher and colleagues[20] 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, ACE inhibitor intake was associated with a 6-fold increase in the incidence of CIN post-procedure (odds ratio, 6.16; 95% CI, 2.01 to 18.93). Interestingly, ARBs did not exhibit a similar effect. It has been speculated that ACE inhibitors may confer protection against CIN by counteracting afferent arteriolar vasoconstriction and subsequent medullary ischemia caused by angiotensin II activation after contrast medium administration. A study by Gupta and coworkers[21] in India randomized patients to captopril, 25 mg 3 times per day for 3 days (starting 1 hour prior to contrast administration) and found a 79% risk

reduction in developing CIN compared to controls who received no therapy. Patients with moderate renal impairment treated with ACE inhibitors were ever reported to have no significant change in their serum creatinine 48 hours after procedure compared with patients not receiving ACE inhibitors.

The study by Rosenstock and coworkers[22] reported 283 patients on chronic ACE inhibitor therapy with chronic kidney disease (GFR, 15 mL/min to 60 mL/min per 1.73 m2). They divided their study population into three groups: chronic ACE inhibitor users who continued ACE inhibitor therapy through the procedure (n = 113), chronic ACE inhibitor users who discontinued ACE inhibitors prior to the procedure (n = 107), and ACE inhibitor naive patients (n = 63). The authors found no significant differences between the groups in the incidence of CIN: continuation group, 6.2%; discontinuation group, 3.7%; and naive group, 6.3% (P = .66). They concluded that ACE inhibitors do not increase the incidence of CIN. They recommended not withholding ACEIs prior to contrast exposure. Dangas and colleagues[7] illustrated a protective effect of RAAS blockade in patients with chronic kidney disease. In a retrospective study of 7230 patients undergoing percutaneous coronary intervention and found that preprocedural ACE inhibition resulted in a lower risk of CIN in patients with chronic kidney disease but not in those with relatively normal renal function.

A recent meta-analysis[23] identified 7 randomized controlled studies enrolling 792 patients undergoing intravascular angiography. There were 297 patients with diabetes mellitus. The overall pooled odds ratio for development of CIN using a fixed-effects model was 0.62 (95% CI, 0.37 to 1.03, P = .06), suggesting a trend towards a reduction in CIN with ACE inhibitors. The overall pooled odds ratio for development of CIN in the diabetes subgroup using a random-effects model was 0.21 (95% CI, 0.06 to 0.71, P = .01), suggesting a significant reduction in CIN with ACE inhibitors. In this meta-analysis, they did not find clear evidence of overall benefit associated with the use of ACE inhibitors to prevent CIN. However, patients treated with ACE inhibitors had a lower mean creatinine (difference in mean difference of serum creatinine, -0.07 mg/dL; 95% CI, -0.10 to -0.04) and a trend toward a reduction in CIN compared with control patients (odds ratio, 0.62; 95% CI, 0.37 to 1.03).

In conclusion, CIN is a known complication after coronary angiography or cardiac catheterization and percutaneous coronary intervention. There are several reversible risk factors that mitigate the likelihood of developing CIN. Patients who experience acute kidney injury have an increased mortality rate when compared to those who retain normal renal function. Preventive measures such as intravenous hydration, acetylcysteine, use of low osmolar nonionic contrast agents, calcium channel blockers, dopamine, and fenoldapam have been used with variable success.[24] The presence of different conclusions can result from significant differences in methodology, study populations, and interventions.

The data regarding ACE inhibitors and CIN are conflicting. There have been studies that report a protective effect, studies that report a negative effect and studies that report no effect. Spatz and colleagues' report[15] is in favor of more benefit for RAAS blockade for preventing CIN. Based on the data presented by other studies; there is no definite correlation between ACE inhibitors and the occurrence of CIN even in subgroup of patients with CKD. So discontinuing ACE inhibitors or ARB before coronary angiography or percutaneous coronary intervention will not probably decrease the incidence of CIN and starting ACE inhibitors or ARB for the reason of lowering the risk of CIN cannot be recommended based on the current literature. As the role of ACE inhibitors in CIN is paradoxical and due to widespread indication in clinical practices before contrast media administration, larger randomized controlled trials are required to further investigate the role of ACE inhibitors and ARB in the development of CIN.

CONFLICT OF INTEREST

None declared.

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Assessment of Peripheral Vascular Disease in Patients With Chronic Kidney Disease

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Cardiovascular disease (CVD) is the leading cause of death and a major cause of morbidity in patients with chronic kidney disease (CKD).[1] Multiple indexes are used to predict severity and prognosis