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Contrast-Induced Nephropathy

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Abstract

With the worldwide increase in the incidence of atherosclerotic coronary artery disease, the rate of coronary interventions has increased. One of the serious complications of this procedure is contrast-induced nephropathy (CIN). This complication can lead to poor outcomes, with an increase in morbidity and mortality of patients. The pathophysiology and risk factors for the occurrence of contrast-induced nephropathy are several and interconnected. The most proposed management of this entity is prophylaxis and thus avoidance of its occurrence. We will take a deeper look on the pathophysiology, the mechanisms by which this complication is aggravated, and how to expect and manage such a problem.

Keywords: coronary intervention, contrast, nephropathy

1. Introduction

Contrast-induced nephropathy (CIN) is a grave complication of angiographic procedures and arises from administration of iodinated contrast media (CM) [1]. CIN is the third most common cause of hospital acquired acute renal injury representing about 12% of the cases. The incidence of CIN varies from 0 to 24% depending on the patient's risk factors [2]. It is generally a transient and reversible state of acute renal failure [3]. However, the development of CIN is linked to a more prolonged hospital stay, an increased morbidity and mortality, and a high health-care cost. Treatment of CIN is predominantly of supportive nature, consisting of calculated fluid and electrolyte management; however, dialysis may be required in some cases [3].

2. Definition

Clinical and experimental studies have used different laboratory parameters to define CIN [4, 5]. Currently, CIN is most commonly defined when either of the following occur within 48 h after contrast administration and persisting for 2–5 days [6, 7]:

- A 25% increase in serum creatinine (SCr) concentration from baseline value
- An absolute increase in SCr of at least 0.5 mg/dL (44.2 $\mu\text{mol/L}$)

3. Epidemiology

CIN is one of the most significant causes of hospital-acquired acute kidney injury (AKI) [8] and presents about 12% of the cases [9]. It represents the third most common cause after renal hypoperfusion (42%) and postoperative renal injury (18%). The reported incidence of CIN following percutaneous coronary intervention (PCI) lies between 0 and 24%. This depends on the associated risk factors, with the greatest incidence being reported after emergency PCI [10, 11]. A meta-analysis which included 40 studies showed a 6% incidence of CIN following contrast-enhanced computed tomography (CT) [12], 9% following peripheral angiography [3], and 4% following intravenous pyelography [13]. The incidence of CIN is low in patients with normal renal function (0–5%) [14]. However, there is an incidence of 12–27% in patients having preexisting renal impairment [15]. Moreover, in one study, an incidence as high as 50% was found in patients with diabetic nephropathy undergoing coronary angiography despite the use of low-osmolar CM (LOCM) and adequate hydration. Also, up to 15% of them needed dialysis [16]. Development of CIN is associated with a longer duration of hospital stay and an increased morbidity and mortality, in addition to more costs [1, 17]. Elevation of post-PCI serum creatinine may have prognostic significance regardless of the initial kidney functions. In fact, a slight elevation in serum creatinine (25–35 µmol/l) is associated with an increase in 30-day mortality [18]. Furthermore, post-PCI serum creatinine elevation has been reported to be linked to higher 1-year mortality than periprocedural myocardial necrosis [19].

4. Risk factors

Mild, transient decreases in GFR occur after contrast administration in nearly all patients. The development of clinically significant acute renal failure depends very much upon the presence or absence of certain risk factors (**Table 1**); factors that increase the incidence of development of CIN are linked to the patient’s comorbid conditions, the procedure to be performed, and the nature of the contrast agents [21].

4.1 Preexisting renal disease

Preexisting renal disease with an elevated basal level of serum creatinine is the most important risk factor for the occurrence of CIN. The incidence of CIN in patients with preexisting chronic kidney disease is extremely high, ranging from

Degree of risk	Nonmodifiable risk factors	Modifiable risk factors
Major	Preexisting renal disease Diabetes mellitus	Osmolality and ionic content of contrast medium Volume of contrast medium administered Repeated exposure to contrast medium
Minor	Age Gender Reduced ejection fraction Congestive heart failure Hypertension	Dehydration Myocardial infarction less than 24 h before angiography Circulatory collapse Anemia

Table 1.
Common risk factors for contrast nephropathy after coronary angiography [20].

14.8 to 55% [20]. As depicted in a study, despite pre-procedure adequate hydration and the use of nonionic CM, CIN happened in one-third of the 439 patients who underwent PCI and had basal creatinine level more than or equal to 1.8 mg/dl [22]. The higher the basal serum creatinine level, the greater the risk of developing CIN. As seen in a study, if basal serum creatinine level is estimated to be ≤ 1.2 mg/dl, the risk of development of CIN is just 2% [23]. In patients with values of creatinine in the range of 1.4–1.9 mg/dl, the risk of CIN in comparison with that in the previous group increases fivefold (10.4%) [23]. Regarding patients with baseline serum creatinine more than or equal to 2.0 mg/dl, 62% of them developed CIN [24]. However, baseline creatinine is not reliable enough for the determination of patients who are at risk for CIN. This arises due to the variation on the basis of gender, age, and muscular mass. For instance, a normal serum creatinine value probably correlates with a moderate decrease in renal function. In order to properly evaluate renal function, assessment of creatinine clearance should be done. The direct measurement of the creatinine clearance is not practical to be done; however, its estimation based on the Cockcroft-Gault formula or Modification of Diet in Renal Disease equation can be easily performed. Multiple studies have proven that an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m² is a cutoff value for considering patients at high risk for the development of CIN. Thus, the estimation of GFR is crucial for CIN risk assessment [25].

4.2 Diabetes mellitus

Diabetic patients represent a very important proportion of those undergoing contrast exposures due not only to the prevalence of diabetes in the general population but also the ability of the disease to cause a wide spectrum of diseases which require radiological procedures using contrast media. The incidence of CIN in diabetic patients varies from 5.7 to 29.4% [26]. Importantly, in diabetic patients with preserved renal function and without other risk factors, the rates of CIN are approximately equal to those of a nondiabetic population [27], while clinically important CIN mostly happens in a group of diabetics with preexisting renal impairment [27].

4.3 Age

Several studies showed that older age is an independent predictor of CIN [28]. The reasons for higher risk are multifactorial, which encompasses age-related changes in renal function including decreased glomerular filtration rate, renal concentration ability, and tubular secretion. The presence of multi-vessel coronary artery disease, mandating complex more prolonged PCI, combined with more difficult vascular access that results from tortuosity and calcification of the vessels that frequently requires a greater amount of contrast, and therefore represent additional factors of elevated CIN risk in elderly.

4.4 Gender

Ovarian hormones can have an influence upon the renin-angiotensin system as well as the renal blood flow. In a retrospective study of 8628 patients who underwent PCI, female sex presented an independent risk predictor of CIN (OR = 1.4, $p < 0.0001$). One-year analyses of outcomes by gender demonstrated a higher mortality rate when compared to males in a cohort of CIN patients (14 vs 10%, $p = 0.05$) [29].

4.5 Heart failure

Advanced congestive heart failure (New York Heart Association class III or IV), reduced left ventricular ejection fraction, or any history of congestive heart failure are independent predictors of CIN and contribute to a greater risk in patients who have diabetes or renal disease. The risk arises as a result of decreased renal blood flow due to low cardiac output in those patients. Moreover, the risk is enhanced by this population's use of specific medications such as aspirin, diuretics, and angiotensin converting enzyme (ACE) inhibitors [30].

4.6 Anemia

Anemia can cause deterioration of renal ischemia which can be an acceptable explanation for the higher incidence of contrast-induced nephropathy in patients with a lower hematocrit level. A baseline hematocrit value of less than 39% for men and less than 36% for women is considered a risk that leads to a higher incidence of CIN. This relation was investigated in a prospective study of 6773 patients who underwent PCI [31]. A lower basal hematocrit value was an independent risk predictor of CIN; and every 3% decline in basal hematocrit resulted in a significant increase in the occurrence of CIN in patients with and without chronic kidney disease (11 and 23%, respectively). Dangas et al. showed that the basal hematocrit level is an independent risk factor for the occurrence of CIN among patients with chronic kidney disease (OR = 0.95, $p < 0.00001$) [17].

4.7 Hyperuricemia

Contrast media have a uricosuric effect, which is caused by increased renal tubular secretion of uric acid. Moreover, hyperuricemia is accompanied by an activated renin-angiotensin-aldosterone system, enhanced synthesis of reactive oxygen species, increased endothelin-1, tubular obstruction by uric acid, and an inhibited nitric oxide synthesis that provokes the development of CIN [32].

4.8 Hypercholesterolemia

Altered nitric oxide-dependent renal vasodilatation is common in hypercholesterolemia. Hypercholesterolemia enhanced the occurrence of CIN through the reduced production of nitric oxide [24].

4.9 Hypovolemia

Hypovolemia leads to active sodium reabsorption, which is an oxygen-dependent process, and increases neurohumoral vasoconstrictive stimuli that can diminish medullary oxygenation. The toxic actions of contrast media on the renal tubular lumen can be exaggerated in hypovolemia. Decreased circulatory volume and renal perfusion augment vasoconstriction of renal vasculature after administration of CM. Volume expansion decreases the activity of the renin-angiotensin system, increases the perfusion of the medulla, and minimizes the elevation in blood viscosity and osmolality. Currently, the most effective preventive measure against the development of CIN is proper hydration [33].

4.10 Hypertension

The alteration in intrarenal expression of vasoactive mediators, mainly renin-angiotensin system and nitric oxide, is a common cause that ranks hypertension as

an important risk factor for CIN. Impaired nitric oxide-dependent renal vasodilatation is common in individuals who are hypertensive. In addition, a decreased nephron count could predispose hypertensive patients to CIN.

4.11 Nephrotoxic drugs

Nephrotoxic drugs that inhibit the vasodilatory effects of prostaglandins make the kidneys extremely vulnerable to the toxic effect of contrast media. Aminoglycosides, sulfonamides, and their combinations with furosemide are very risky. Cyclosporin A may intensify medullary hypoxia, and cisplatin can bind to sulfhydryl groups. Mannitol can increase the metabolic load and the oxygen consumption of the kidney, and amphotericin B can cause the combined effect of mannitol and cyclosporine A. It has been demonstrated that nonselective NSAIDs and selective COX-2 inhibitors decrease the availability of vasodilatory prostaglandins in the kidneys and enhance the vasoconstrictive effect of CM [34].

4.12 ACE inhibitors and angiotensin receptor blockers

ACE inhibitors have been identified as a risk factor for CIN because of their ability to reduce renal function. On the contrary, some small studies have shown that the inhibition of angiotensin II can decrease renal vasoconstriction following the injection of contrast media. In a randomized controlled study including 71 patients with diabetes who underwent coronary angiography and randomized to captopril (25 mg thrice daily) or control, there was a significant decrease in CIN in the patients who received captopril compared with the control group (6 vs 29%, respectively, $p < 0.02$) [35]. A randomized controlled study was performed on 80 patients with serum creatinine less than 2 mg/dl who underwent coronary angiography where captopril was administered in 48 patients preceding coronary angiography. CIN occurred in five patients (10.4%) in the captopril group, compared with only one patient (3.1%) in the control group ($p = 0.02$) [36]. We can say that holding ACE inhibitor or ARB use before coronary angiography is to be considered.

4.13 Acute myocardial infarction

A study by Rihal and his colleagues pointed that acute myocardial infarction occurring within 24 h before administration of the CM is a risk predictor to CIN (OR = 1.85, $p = 0.0006$). This study showed that CIN represents a frequent complication in acute myocardial infarction. This can occur, as well, in patients with a normal baseline renal function [30]. In 2082 percutaneous interventions for acute myocardial infarction, a more than sevenfold (3.2 vs 23.3%) elevation in 1-year mortality in patients who acquired CIN was acknowledged [37].

4.14 Contrast medium-related risk factors

4.14.1 Increased dose of contrast medium

Based upon multiple sources, the relatively unhazardous cutoff point of contrast amount ranges from 70 mL up to 220 mL. However, very small doses as much as 20–30 mL are capable of inducing CIN. In a study that included patients performing coronary angiography, each 100 mL of contrast medium administered was linked to a significant increase of 12% in the risk of CIN (OR = 1.12, $p = 0.02$) [32]. A clear accepted dose is four times the creatinine clearance.

4.14.2 High-osmolar and ionic CM

Most side effects attributable to contrast media are linked to its hypertonicity. Currently, four main types of contrast media are used in practice today, including nonionic low-osmolar, ionic low-osmolar, nonionic iso-osmolar, and ionic high-osmolar contrast media. In a large study which compared the nonionic low-osmolality agent iohexol to the ionic high-osmolality agent meglumine/sodium diatrizoate in patients with preexisting renal impairment undergoing angiography, patients with renal impairment who received diatrizoate were 3.3 times more liable to develop CIN in comparison with those receiving iohexol [38]. NEPHRIC trial is a randomized, prospective study that made a comparison between the nonionic iso-osmolar CM iodixanol with the nonionic low-osmolar CM iohexol in 129 patients with renal impairment and diabetes undergoing coronary or aortofemoral angiography. The incidence of CIN was 3% in the iodixanol group and 26% in the iohexol group ($p = 0.002$) [39]. In one other randomized study, the incidence of CIN provoked by iodixanol and iohexol was compared in 124 patients with basal creatinine level >1.7 mg/dl. The incidence of CIN was 3.7% in iodixanol group and 10% in iohexol group ($p > 0.05$) [17]. In addition, CM are classified as ionic and nonionic. A randomized trial of 1196 patients performing coronary angiography showed that nonionic CM lowered the incidence of CIN in patients with preexisting renal impairment [38]. In high-risk patients, it is better to avoid the use the high-osmolar and ionic CM to lower the risk of CIN.

5. Pathophysiology

No definitive causative has been defined as regards the pathogenesis of CIN in the literature. The most accepted theory for the development of CIN following contrast administration relies upon the vasoconstriction of the vessels in the renal medulla leading to reduced oxygen delivery [40]. Reduced oxygen delivery and prolonged vasoconstriction leads to enhanced production of oxygen-free radicals like hydrogen peroxide and superoxide leading to increased damage [41]. Other suggested causes of this condition are elevated blood viscosity, reperfusion injury, direct toxic damage to the cells, and the release of dopamine, angiotensin II, and vasopressin. These factors induce further vasoconstriction and damage the renal function [42]. The use of supportive therapy in critically ill patients, for instance, the mechanical ventilation and inotropic drugs, and the variable health risks this group of patients have as anemia and sepsis have been shown to increase additional kidney damage resulting from vasoconstriction and hypoxia [43].

5.1 Regional hypoxia as a cause of contrast-induced nephropathy (CIN)

Renal perfusion is very high in the cortex. The medullary portions are maintained at the border of hypoxia such that pO_2 levels can be as low as 20 mmHg [44]. This is the price for maintaining the countercurrent mechanism used for the control of urine excretion. A vulnerable kidney region is the deeper part of the outer medulla, an area far from the vasa recta which supply the renal medulla with blood. It is there where the thick ascending limbs of the loop of Henle encounter hypoxic damage [45]. The cause for the vulnerability of the outer medullary portion of the nephron is the relatively higher oxygen needs due to salt reabsorption. The addition of contrast media to the medium augments the hypoxic injury imposed upon this region by increasing the renal vascular resistance, as seen in the rat model [46]. A second factor that has been postulated to mediate CIN is

an elevated oxygen demand due to an enhanced workload in the tubular cells. First, there is a temporary increase in GFR that follows giving contrast media [47], and second, osmotic diuresis may reduce the para-cellular absorption of the proximal tubular cells, causing a greater load of NaCl that has to be absorbed in the distal tubules. Liss et al. [48] have shown that contrast media can enhance medullary blood flow to the kidney, although pO₂ decreases, which is supported also by a study of Heyman et al. [49]. These two studies suggest that an increased oxygen demand has taken place following contrast media injection. Local kidney hypoxia can be augmented by the systemic effects of some contrast media, such as transiently diminished cardiac output [50] and abnormal pulmonary ventilation-perfusion relationship [51]. Also, the amount of oxygen delivered to the peripheral tissues might be impaired, since contrast media can increase oxygen affinity of hemoglobin [52]. If renal outer medullary hypoxia causes CIN, the blockade of the transporters in this portion of the nephron must have helpful effects on its prevention. The major part of the transport that occurs in the medullary thick ascending limb is the Na-K⁺-2Cl⁻ cotransporter, which, as mentioned above, is blocked by furosemide. Blocking this transport would significantly decrease the local oxygen consumption.

5.2 Radiocontrast-mediated changes in renal blood supply

Renal blood flow and intrarenal microcirculation are markedly altered by contrast medium (CM) [53]. The extent and distribution of renal hemodynamic changes depends on the species investigated as well as on the type, volume, and rate of contrast administration. Moreover, renal hemodynamic effects of CM gravely depend on the hydration state and on additional predisposing factors that may have an effect on the renal circulation and the tone of the renal vasculature, such as chronic renal disease, diabetes mellitus, senility, and inflammation. In an early study in dogs subjected to a high-osmolar CM, total renal blood flow was transiently enhanced for 5–15 min, followed by a decline by 25% below baseline, reaching beyond a couple of hours [54]. In healthy humans, renal blood flow fell 8% over 30 min after the intravenous administration of conventional doses of CM [53]. On the contrary, in patients with chronic kidney disease undergoing coronary angiography, a transient short augmentation of renal blood flow was followed by a dramatic 40% decline, lasting for more than 3 h [54].

5.3 Cytotoxic effects on renal tubular cells

Investigations performed in vitro on cell lines are used to assess the renal tubular cell function or damage. A porcine cell line of renal proximal tubules, LLC-PK1, was used by Hardiek et al. [55] to investigate the occurrence of CIN. An effect on apoptosis was not elucidated, even though proliferation was impaired. Diminished proliferation will have a hazardous effect on renal function with a delay of hours to days, which may help in explaining the course of CIN. Independent of the contrast media used, tubular cell damage can occur. A more specific distortion of proximal tubular function seems to be a perturbation of mitochondrial enzymatic activity and mitochondrial membrane potential [56]. The degree of mitochondrial enzymatic activity impairment depends mainly on two features of the contrast media: the ionic nature as well as the molecular structure. Remarkably, low-osmolar contrast media had the least observed effects, followed by the iso-osmolar contrast media. Ionic compounds showed the most deleterious effects [56]. In the distal tubule, contrast media may trigger apoptotic effects in the cells, as depicted in the Madin-Darby canine kidney (MDCK) cell line model [57].

5.4 Generation of oxygen-free radicals

Among the often-discussed mechanisms, superoxide and other reactive oxygen species (ROS) have been discussed to be an aggravating factor for CIN. Oxygen free radicals are endogenously produced, and levels can increase during oxidative stress. The commonest oxygen radicals are superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-) [58]. O_2^- and OH^- are more reactive in comparison with H_2O_2 , which is not a radical but shows greater membrane permeability. O_2^- rapidly scavenges nitric oxide (NO) and could diminish NO activity in the renal vessels. Since NO decreases oxygen consumption, it is considerable to speculate that decreased (scavenged) NO levels in diabetes increases oxygen consumption, thus leading to reduced partial oxygen pressure values with consequences for endothelial-epithelial structure and function. ROS can play a role in the effects of various vasoconstrictors that are considered necessary for the development of CIN. Because ROS are extracellular signaling molecules, they can have a crucial role in mediating the effects of vasoconstrictors, such as thromboxane A₂, angiotensin II, adenosine, endothelin (ET)-1, and norepinephrine. The adverse effects of CM on kidney function can therefore involve the generation of ROS, for example, via adenosine formation. This idea is supported by experiments in which the generation of ROS was inhibited by allopurinol or the amount of ROS was decreased by O_2^- dismutase. In these models, CM-induced reductions in glomerular filtration rate are attenuated [59].

6. Preventive measures against contrast-induced nephropathy

6.1 Adequate hydration

6.1.1 Intravenous hydration

Adequate hydration for patients performing CM-enhanced imaging studies was suggested approximately 40 years ago [30]. The beneficial effects of hydration were initially reported in the early 1980s by studies that compared outcomes of hydrated patients with historical controls [60, 61]. These reports were supported by the first RCT in 1994, concluding that patients with chronic renal impairment benefit better from intravenous (0.45%) saline administration (for 12 h before and 12 h after angiography) in comparison with saline plus mannitol or furosemide [62]. Since then, multiple RCTs have assured the benefit of intravenous normal saline (0.9%) hydration that is started 12 h preceding to 12 h after CM injection [63–65] in the prevention against CIN over 0.45% saline [65] or a fluid bolus (300 mL) during CM administration only [66]. The rate of infusion was reported as 1 mL/kg/h [67]. CM safety committee endorse a regime of intravenous infusion of 1.0–1.5 mL/kg/h for at least 6 h before and after CM administration [68].

6.1.2 Oral hydration

In order to overcome the limitations of outpatient intravenous hydration, investigators have assessed the use of pre-procedure oral hydration followed by post-procedure intravenous hydration in patients who are admitted for catheterization on the day of procedure. In an RCT on patients with mild-to-moderate renal insufficiency, Taylor et al. reported an effective protocol which includes pre-angiography oral hydration (1000 mL clear fluids over 10 h) that is followed by 6 h of intravenous hydration (0.45% normal saline solution at 300 mL/h) that starts just before CM

exposure [69]. The results were comparative with overnight intravenous hydration (0.45% normal saline solution at 75 mL/h for both 12 h before and after angiography). A limitation of this protocol can be high infusion rate (300 mL/h) post-procedure for the patients having left ventricular impairment. Trivedi and his colleagues demonstrated different results as they observed that patients with unrestricted oral hydration had more opportunities of acute renal impairment compared to those receiving normal saline for 24 h (at a rate of 1 mL/kg/h) beginning 12 h before the scheduled catheterization ($p = 0.005$) [68]. In this study, however, there was no set protocol for oral hydration for patients to follow that probably could have contributed to its ineffectiveness. Later, Dussol et al. randomized 312 patients with chronic kidney disease (CKD) to receive either per oral sodium chloride (NaCl) (dose: 1 g/10 kg bodyweight/day for 2 days before the procedure), intravenous normal saline 15 mL/kg for the 6 h preceding the procedure (control arm), theophylline, or furosemide in addition to the treatment given to patients in the control arm [70]. Oral saline hydration was found to have comparative effectiveness as intravenous saline hydration as regards preventing CI-AKI.

6.1.3 Sodium bicarbonate-based hydration

The acidic pH promotes free radical production (which is found in tubular urine) [71], while elevated pH of normal extracellular fluid inhibits it [72, 73]. Since CM administration escalates the oxidative stress and increases the generation of free radicals and reactive oxygen species (ROS), alkalinizing renal tubular fluid with bicarbonate appears to be a logical strategy to protect against renal injury [74]. As a result of active reabsorption, bicarbonate concentration in the renal tubules lowers (to about 6 mEq/L), and the tubular fluid pH is approximately 6.5 near the end of the proximal tubule in the renal medulla [75]. In the descending loop of Henle, water and chloride are passively reabsorbed. This elevates urine pH to ~7.4 at the tip of the papilla, and this part is spared from contrast nephropathy [76], which suggests that higher pH is protective. Also important is the observation that outer medulla is the most susceptible to CIN [62] and has acidic pH [72] that promotes activity of ROS. Superoxide, a ROS generated by ischemia, might react with medullary NO to produce the potent oxidant peroxynitrite [73]. At physiologic concentrations, bicarbonate scavenges peroxynitrite and other ROSs produced from NO [74]. Thus, several oxidant mechanisms of renal injury might be avoided using sodium bicarbonate. The useful effect of higher proximal tubular pH is approved by a report that acetazolamide, a carbonic-anhydrase inhibitor which blocks proximal tubular bicarbonate reabsorption, is protective in contrast-induced renal failure [77]. Merten et al. reported first study on the use of sodium bicarbonate in humans as a nephron-protective agent [78]. Patients received 154 mEq/l of either NaCl (in 5% dextrose H₂O) or sodium bicarbonate (in dextrose H₂O), as a bolus of 3 mL/kg/h for 1 h before iopamidol contrast, followed by an infusion of 1 mL/kg/h for 6 h after the procedure. CIN occurred in 8 patients (13.6%) infused with NaCl but in only 1 (1.7%) of those receiving sodium bicarbonate ($p = 0.02$). Afterwards, many RCTs have compared the efficacy of sodium bicarbonate with saline hydration regarding the prophylaxis against CIN. These have been reviewed in multiple meta-analysis [79–82], which concluded that sodium bicarbonate-based saline hydration is more efficacious to saline hydration only.

6.1.4 Pharmacological prophylaxis

Various drugs have been assessed as prophylactic nephroprotective agents against contrast-induced acute kidney injury (CI-AKI) such as N-acetylcysteine

(NAC) [36, 83], statins [84, 85], ascorbic acid [76, 86], and theophylline [87]. However, only statins have been approved for the prevention against the occurrence of CIN. Currently, the CM safety committee recommends the withdrawal of nephrotoxic drugs before CM administration [85].

6.1.5 N-Acetylcysteine (NAC)

NAC gives protection against CIN by improving the body's antioxidant abilities [88]. In vitro, NAC does this efficiently by scavenging hypochlorous acid as well as reacting with hydroxyl radicals [89]. In vivo due to its extensive degradation, it is likely that any antioxidant effect it exerts would be indirect, most probably by inducing glutathione synthesis. Different studies have suggested that NAC guards against glutathione depletion [90, 91] and elevates renal glutathione levels [92]; the latter has been demonstrated to result in the reduction of renal injury in ischemia reperfusion models [93, 94] and recently in CIN [95, 96]. Glutathione cannot enter the cell; instead, it must be formed inside the cell from glycine, glutamate, and cysteine [97]. Cysteine offers the active HS group which is crucial for the glutathione synthesis and thus is the rate-limiting factor in this process. NAC after deacylation produces cysteine that passes to the renal cells and serves as a precursor for glutathione synthesis. It can also produce vasodilator effects [98]. By ameliorating contrast-induced vasoconstriction, NAC can produce its nephron-protective role [99]. Increase in the medullary blood flow with NAC has also been demonstrated [100, 101]. The first clinical use of NAC for CIN was reported by Tepel et al. [83]. Eighty-three patients who had chronic renal impairment were randomly planned either to take oral NAC (600 mg twice daily) and 0.45% saline intravenously, before and after administration of the CM, or to receive placebo and saline. NAC-receiving patients had lower incidence of CIN. Since then numerous studies have assessed the role of NAC against CIN. Those studies have been done mainly in patients undergoing coronary angiography [102]. Some 17 meta-analyses have been published as regards this subject [76, 86, 87, 103–116], 10 that approve its use (most of which were published early on). Most of these meta-analyses reported vast heterogeneity that makes it difficult to make clinical treatment recommendations relying on the provided data. Recently, results of the largest multicenter RCT of 2308 patients called "Acetylcysteine for Contrast-Induced Nephropathy Trial" (ACT) have been published [36]. It randomized patients in 46 centers in Brazil, to take 1200 mg of oral NAC or placebo twice daily for 2 doses before and after the procedure. Intravenous hydration with normal saline, 1 mL/kg/h, from 6–12 h before to 6–12 h after angiography, was strongly recommended. NAC was not able to significantly reduce the incidence of CIN (12.7% in the NAC group and 12.7% in the control group, $p = 0.97$) [117].

6.1.6 Ascorbic acid

Ascorbic acid serves as an antioxidant [118]. It does this via reacting with most biologically relevant free radicals and oxidants such as superoxide ions and hydroxyl ion [119]. It donates an electron to devastating oxidizing radicals [120]; this one-electron oxidation leads to the formation of AH^{\cdot} the ascorbyl radical also called semidehydroascorbic acid [121]. Consequently, the reactive free radical is reduced [122]. Ascorbic acid has been reported to result in vasodilatation in coronary [123] and brachial arteries [124]. Thus, vitamin C can have favorable effects on vascular dilatation, through its antioxidant actions on nitric oxide, but these findings are not consistent [125]. Through which pathway vitamin C may offer nephron protection against CIN is still currently uninvestigated. The first clinical use of ascorbic

acid for CIN prevention was reported by Spargias and his colleagues [116]. Two hundred and thirty-one patients were summoned and randomized to obtain either 3 g of ascorbic acid supplied in chewable tablets or placebo at least 2 h prior to the beginning of the required procedure. This was followed by 2 g of ascorbic acid or placebo the night and the morning post-procedure. Intravenous hydration with normal saline at a rate of 50–125 mL/h was started in every patient till at least 6 h post-procedure. Incidence of CIN was less in ascorbic acid group (9%) and 20% in control group ($p = 0.02$). A considerable change in the antioxidant state was noticed in the group treated with ascorbic acid. Since then various RCTs have been performed [126, 127]. Pooled analysis of these trials assumed that patients who receive ascorbic acid have 33% less risk of CIN in comparison with patients receiving placebo or alternative pharmacological therapy (RR: 0.67 (95% CI: 0.46–0.96), $p = 0.03$) [100]. This indicates that ascorbic acid provides effective nephron protection in the face of CIN and may form a part of efficient prophylactic pharmacological regimens. However, the utilization of ascorbic acid has not yet been recommended by the contrast media safety committee.

6.2 Statins

Statins maintain nitric oxide formation, lower oxidative stress, and beneficially affect the endothelial function [101]. In one retrospective study of more than 1,000 patients with renal impairment undergoing coronary angiography, the risk of CIN was markedly decreased in patients who are receiving a statin before the procedure [128]. Another study of more than 29,000 patient recorded in a percutaneous cardiac intervention registry demonstrated that patients who received statins before the procedure had both a lower CIN incidence ($p < 0.0001$) and nephropathy that required dialysis ($p < 0.03$) [181]. Further studies looking into the benefit from statins are warranted [129].

6.2.1 High-dose versus low-dose statins

High-dose statin therapy may be theoretically more efficacious regarding CIN prevention as a result of acute suppression of inflammatory chemokines [130]. Xie and his colleagues investigated the potency of high-dose statins (simvastatin 80 mg, atorvastatin 40 and 80 mg) compared with low-dose statins (simvastatin 20 mg, atorvastatin 10 and 20 mg) and revealed that high-dose statins lowered the incidence of CIN [131]. These results were backed up by a recent meta-analysis which showed that high-dose statins (atorvastatin 80 mg, simvastatin 80 mg) in comparison with low-dose statins (atorvastatin 10 and 20 mg, simvastatin 20 mg) in patients having acute coronary syndromes resulted in a relative risk ratio for CIN of 0.46 (4.5 vs 10.2%, $p = 0.004$); however, it was not of considerable significance among patients performing elective procedures [132]. However, high-dose statins are guideline recommended medications to lower the risk of CIN.

6.2.2 Theophylline

Adenosine has been implicated to be a responsible factor for mediating CM-enhanced renal vasoconstriction [133–135]: hence the use of adenosine antagonists appears logical [136]. Theophylline and aminophylline have been often used to measure their efficacy as adenosine receptor antagonists in guarding against contrast-induced acute kidney injury (CI-AKI). Various randomized trials have used theophylline [20, 137, 138]. A meta-analysis of those studies guided to the fact that theophylline considerably lowers the risk of CIN (RR: 0.48; 95% CI: 0.26–0.89;

$p = 0.02$). There was moderate heterogeneity that suggests cautious interpretation of these results. Furthermore, patients with baseline renal insufficiency did not show any benefit from theophylline.

6.2.3 Allopurinol

This drug is a xanthine oxidase inhibitor which may hamper the fall in the GFR following CM exposure by limiting oxygen free radical production, inhibiting adenine nucleotide degradation, and limiting the vasodilator reaction to intrarenal adenosine. A trial that included 159 patients randomized patients performing coronary angiography procedures to allopurinol (300 mg orally) with hydration or hydration alone, showed that allopurinol can guard against CIN in high-risk patients receiving CM [139]. However, these effects of allopurinol in the prevention of CIN need further larger studies.

6.2.4 Dopamine

Dopamine (in a renal dose 0.5–2.5 $\mu\text{g/kg/min}$) has a vasodilator action on the renal vasculature and has an ability to increase renal blood flow and GFR with a potential benefit in the prevention of CIN. Trials with positive results were small, not randomized and with questionable endpoints [140]. On the contrary, negative trials were large, randomized, controlled, and with adequate statistical power [141]. Thus, the usage of dopamine in guarding against CIN is no longer recommended.

6.2.5 Targeted renal therapy

A suggested theory for failure of various drugs used for kidney protection is that systemically administered drugs may not achieve adequate drug level in the renal vasculature in order to be successful regarding the prevention of CIN. This has led to the technique of direct infusion of a drug in a selective manner into the kidneys via the renal arteries, which is known as targeted renal therapy (TRT). This should have the ability of decreasing the systemic side effects of that drug. Fenoldopam is a dopamine-1 agonist that acts as a vasodilator and thus has a potential to attenuate the vasoconstriction induced by CM in the renal vessels. Although it was not possible to demonstrate its benefit in reducing the incidence of CIN [142], it was observed that a large number of patients could not tolerate low doses of fenoldopam as a result of drug-induced hypotension, which is itself a risk predictor of CIN. Employing TRT, selective bilateral renal artery catheterization may be performed for localized drug delivery. In a pilot study on patients undergoing endovascular aneurysm repair, Benephit PV Infusion System (Flow Medica, Inc., Fremont, CA, USA) was used for selective catheterization of both renal arteries through brachial artery puncture. There was no episode of hypotension, thus every patient received fenoldopam at a rate of 0.4 $\mu\text{g/kg/min}$ for the duration of the aneurysm repair [143]. If the pigtail catheter is inserted in the aorta just over the level of the renal artery avoiding selective catheterization, this appears to be a simple way but would lead to considerable systemic drug effects as a result of infusion of the drug into the systemic circulation [143]. The safety and performance of TRT were also assessed by retrospective analysis of 285 patients who received fenoldopam via TRT, as a part of “The Benephit System Renal Infusion Therapy (Be-RITe)” registry [144]. Benephit Infusion System (Flow Medica, Inc., Fremont, CA, USA) was used. Bilateral renal artery cannulation achieved success in 94.2%, with a mean cannulation time of 2 min. Incidence of CIN was 71% less than predicted, with the greatest

benefit in patients with highest risk of CIN. Prospective studies and RCTs are therefore required in order to assess real ability of this technique.

6.2.6 Ischemic preconditioning

Ischemic preconditioning includes exposure to short episodes of ischemia followed by reperfusion to make the target organ prepared against the main ischemic insult. If the site of generation of these short episodes of ischemic reperfusion is remote from the site of target organ, it is called remote ischemic preconditioning. This technique has been used with only variable success in offering myocardial and renal protection in cardiovascular medicine [145–151]. Results of an RCT propose usefulness from remote ischemic preconditioning in preventing CIN [152]. The likely usefulness may arise from its capability to attenuate the CM-induced ischemia reperfusion injury. Recently, ischemic preconditioning has lost its credibility as it was unable to translate successful results in laboratories into clinical practice [153].

7. Sequelae

Patients who develop CIN have greater complications, a worse prognosis, more serious long-term outcomes, and longer duration of hospital stay, which result in elevated medical costs [154, 155]. Less than 0.5–2% of patients who develop CIN require dialysis [156]. Those requiring dialysis are more likely to exhibit serious short- and long-term outcomes. Nearly 30% of those patients experience chronic renal impairment [154]. CIN may also be linked to an increased mortality which is independent of other risk factors [157]. Hospital death rates in such patients have been reported as 36% and the 2-year survival rate as only 19% [158, 159]. Levy et al. compared 181 inpatients that developed CIN with matched control patients who did not develop it; both groups underwent contrast-related procedures [156]. The mortality rate in the control group was 7%, compared to 34% in the CIN group. In another study of 7230 patients who underwent percutaneous coronary interventions, patients who developed CIN had more common myocardial infarctions, more hospital stays, and higher 1-year mortality rates compared to those without CIN. CIN patients are more likely to have target vessel revascularization after 1 year, bypass surgery, bleeding which mandates transfusion, and various vascular complications [160]. Patients who undergo a primary percutaneous intervention for acute myocardial infarction and the procedure complicates by CIN were reported to be significantly more likely to have major complications within hospital admission such as acute pulmonary edema, the need for pacemaker insertion, cardiogenic shock, and respiratory failure [160]. Patients with renal insufficiency are at more significant risk of developing atherosclerosis [19]. Actually, following a contrast procedure, a rise in serum creatinine is a more significant indicator of late mortality compared to an elevated creatine kinase-MB isoenzyme [160].

8. Conclusion

Contrast-induced nephropathy is not an uncommon sequela of coronary angioplasty. It can lead to increased morbidity and mortality. One should be aware of the risk factors that increase its incidence and thus limit the amount of contrast so as to avoid such a deleterious complication. Prevention is better than treatment in this case.

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