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Review Article

Contrast induced nephropathy

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Abstract: Contrast-induced nephropathy is an important source of hospital morbidity and mortality due to ever-increasing use of iodinated contrast media in diagnostic imaging and interventional procedures. It is considered as the third most common cause of hospital-acquired acute renal failure, after surgery and hypotension. At present, no available treatment can reverse or ameliorate contrast induced nephropathy once it occurs, but prophylaxis is possible. This review will help clinicians to recognize predisposing risk factors, to institute appropriate prophylactic treatments, and to have knowledge of the clinical presentation and management of the condition.
Keywords: Acute kidney injury, contrast induced nephropathy, iodinated contrast media, N acetylcysteine

INTRODUCTION

Due to increasing availability and technical advancement in interventional procedures, an enormous number of patients are being exposed to iodinated contrast agents [1]. This, along with routine use of contrast agents in imaging modalities, exposes ever-increasing number of patients to risks associated with use of these agents, including contrast induced nephropathy (CIN) which is the third leading cause of hospital-acquired acute renal failure, after surgery and hypotension, accounting for 12% cases [2]. Although its incidence is low in patients with normal renal function, it can be much higher in those with pre-existing risk factors. It is important for physicians and radiologists to have in-depth knowledge of predisposing risk factors, preventive strategies, and management of this condition.

Definition

The term contrast media nephrotoxicity is widely used to refer to the reduction in renal function induced by contrast media. The most widely used definition, provided by EUSR guidelines, implies: Impairment in renal function (an increase in serum creatinine by more than 25% or 44 µmol/ L) occurring within 3 days following the intravascular administration of contrast media and the absence of alternative etiology [3]. Ideally, the impairment of renal function should be measured by serial creatinine clearance since single time measurement of serum creatinine level may be much less sensitive parameter than creatinine clearance [5]. There is a felt need for new criteria for early and accurate diagnosis of CIN.

Incidence of CIN

The incidence of CIN varies markedly, depending on the definition used and on characteristics of patient population studied, including pre-existing risk factors. An overall incidence of 14.5% was quoted by McCullough *et al*. [4]. Incidence among patients with diabetes has been reported to be 9 to 40% in patients with mild-to-moderate chronic renal insufficiency and 50 to 90% in those with severe chronic renal insufficiency [6, 7]. In contrast, the incidence in the general population is much lower and has been calculated to be less than 2% [8]. Despite a lack of consensus as to exact rates and definitions, CIN remains a significant source of morbidity and mortality. McCullough *et al*. [4] found that in-hospital mortality rates were 1.1% for patients with no CIN compared with 7.1% for those with nephropathy alone, and up to 35.7% for those with nephropathy requiring dialysis.

Pathogenesis

The exact underlying mechanisms of nephrotoxicity have yet to be fully elucidated but are

likely to involve the interplay of several pathogenic factors. Intrinsic causes include the following: increased vasoconstrictive forces, decreased local prostaglandin- and nitric oxide (NO)-mediated vasodilatation, a direct toxic effect on renal tubular cells with damage caused by oxygen free radicals, increased oxygen consumption, and increased intra tubular pressure secondary to contrast-induced diuresis, increased urinary viscosity, and tubular obstruction, all culminating in renal medulla ischemia [9,10]. Intrinsic causes act in concert with harmful extrinsic (pre renal) causes such as dehydration and decreased effective intravascular volume. Also, there is evidence that these agents are directly toxic to the cells.

Risk factors

Many factors have been reported as influencing contrast-induced nephropathy (Table 1), but few have been proven to be independent risk factors. However, it has been recommended that every known risk factor should be analyzed to properly evaluate a total cumulative risk of developing contrast-induced nephropathy because total risk rises as the number of risk factors increase.

Age

The elderly are at increased risk of CIN with reported incidence of 11% in patients older than 70 years [11]. The reasons for higher risk of developing CIN in the elderly probably are multifactorial, including age-related decline in eGFR, tubular secretion and concentration ability, as well as more difficult vascular access requiring greater amount of contrast, presence of multi-vessel disease, etc.

Renal insufficiency

Irrespective of cause, preexisting impairment of renal function appears to be the most important risk factor [12]. A comprehensive review by Berns *et al*., attributed baseline renal insufficiency as a major risk factor for the development of CIN, in 60% of cases [13]. The risk of CIN is inversely related to the calculated estimated GFR (eGFR). Patients with stage III CKD or more, according to K/DOQI guidelines, are at higher risk for developing CIN. In a study by Moore *et al*. [14], highly significant relationship ($p< 0.001$) was discovered between an increasing baseline level of serum creatinine and the frequency of nephrotoxicity (varying from 2% in those with baseline creatinine of < 1.5 mg/dL to 20% in those with levels of > 2.5 mg/dL).

Diabetes mellitus

Diabetes mellitus with associated renal insufficiency has been identified as a one of the most important risk factor for contrast nephropathy [4, 11]. Given the high prevalence of diabetes in the general population and its ability to cause broad spectrum of cardiovascular diseases, which require radiological procedures for their diagnosis and treatment, diabetic patients represent a significant proportion of those undergoing contrast exposure. Patients with diabetic nephropathy have a greater risk for contrast-induced nephropathy than non diabetic patients with similar levels of preexisting renal insufficiency and have higher incidence of oliguria and need for dialysis [13, 15]. In addition, patients with diabetes who have advanced CKD (serum creatinine levels > 3.5 mg/dL) due to causes other than diabetic nephropathy are at significantly higher risk of developing CIN [7]. Moreover, when patients in this high-risk group develop nephropathy, they more often develop oliguria and need dialysis [7].

The role of diabetes itself, as an independent risk factor for the development of contrast-induced nephropathy, is not clear, yet. Earlier studies failed to corroborate this connection [12, 13, 15]. For example, in study by Parfrey *et al*. [12], none of 85 patients with diabetes and normal renal function developed clinically significant renal impairment. However, in a recent study by Toprak *et a*l. [16], a total of 421 patients with CKD stage III and IV were divided into three groups: diabetes mellitus (n=137; glucose ≥126 mg/dL), pre-diabetes (n=140; glucose between 100 and 125 mg/dL), and normal fasting glucose (n=144; glucose < 100 mg/ dL). CIN, defined as an increase of ≥25% in creatinine baseline within 48 hr of angiography, occurred in 20% of diabetics, 11.4% of pre-diabetics, and 5.5% of patients with normal fasting glucose level.

Recently a study by Turcot *et al*. [17]; revealed elevated serum glucose level (>150 mg %) as independent risk factor for development of CIN (42% vs5.3%, p= 0.01)

Nephrotoxic Drugs

It is anticipated that concomitant use of nephrotoxic drug and contrast administration will increase risk of CIN. Directly nephrotoxic drugs (e.g., cyclosporine A, aminoglycosides, amphotericin, and cisplatin), nonsteroidal antiinflammatory drugs [NSAIDs] and diuretics especially furosemide (due to intravascular volume depletion), have been reported to aggravate contrast agents induced kidney injury [18, 19]. Although all these medications are known to induce renal damage, their individual roles as independent risk factors of contrast-induced nephropathy have yet to be determined in large prospective clinical trials.

Reduction of Effective Intravascular Volume

Reduction of effective intravascular volume (due to congestive heart failure, liver cirrhosis, or abnormal fluid losses), prolonged hypotension (especially when induced by diuretics, most notably furosemide), and dehydration have been reported as

contributing to prerenal reduction in renal perfusion, thus enhancing the ischemic insult of contrast media [15,19].

Multiple Myeloma

Importance of multiple myeloma as risk factor declined after a review of retrospective studies by McCarthy and Becker [20], which revealed an incidence of only 0.6% to 1.25%, indicating that this group is not at increased risk with modern contrast agents, provided that volume expansion is achieved at the time of exposure.

Contrast agent's related factors

Large doses and multiple injections of contrast media within 72 hr increase the risk of the patient's developing contrast-induced nephropathy [18, 21].However, cut-off values have not been defined, yet. Similarly, the route of administration is also important, with contrast media being more nephrotoxic when administered intraarterially. This effect is thought to be due to the fact that the acute intrarenal concentration of contrast media is much higher after intraarterial rather than IV injection.

More importantly, the osmolarity of the contrast media has significant impact on occurrence of CIN, with large clinical studies and meta-analyses indicating that the use of an LOCM substantially reduces the risk of nephropathy in high-risk patients compared with the use of HOCM [14, 22-31]. LOCM causes less discomfort and fewer cardiovascular and anaphylactic adverse reactions than HOCM but is more expensive. It has been recommended that a high risk for development of contrast-induced nephropathy be considered one of the indications for the use of LOCM or IOCM, whereas in patients with normal renal function and no risk factors present, no advantage over the traditional HOCM has been shown.

Anemia

In a large registry of 6,773 consecutive patients treated with PCI, low baseline hematocrit was identified as an independent predictor of CIN by multivariate analysis [32].

Cumulative risk assessment

Since occurrence of CIN is highly related to presence of preprocedural risk factors, many attempts have been made to develop a risk assessment score. The European Society of Urogenital Radiology [3] recommends that only elevated serum creatinine levels (particularly secondary to diabetic nephropathy), dehydration, congestive heart failure, age greater than 70 years, and concurrent nephrotoxic drugs be used to establish risk. However, the use of a more comprehensive preprocedural assessment may be warranted, particularly in the high-risk in-hospital population.

Mehran *et al*. developed single risk score for prediction of CIN in patients after PCI [33], which consist of eight variables-

- Presence of hypotension
- Use of Intra-aortic balloon pulsation
- Congestive heart failure
- Age >75 years
- Presence of diabetes
- Anemia
- Volume of contrast injected
- Baseline serum creatinine.

Preventive Measures

Hydration

Hydration is a universally accepted component of protocols for preventing CIN [19, 34]. The theoretical rationale for hydration is that it should decrease the activity of the renin-angiotensin system, reduce the levels of other vasoconstrictive hormones such as endothelin, increase sodium diuresis, decrease tubuloglomerular feedback, prevent tubular obstruction, protect against reactive oxygen species, and dilute the contrast media in the tubule, thus decreasing any direct nephrotoxic effect of the contrast agent on the tubular epithelium. Despite the fact that no controlled randomized trial with sufficient statistical power has been rigorously performed to prove the benefit of hydration as scientific fact, it is almost universally accepted as an appropriate and safe measure to prevent contrast-induced nephropathy.

The beneficial effect of adequate hydration in reducing rates of CIN was established in the randomized study of Solomon *et al*. [19], conducted on 78 patients with chronic renal insufficiency undergoing coronary angiography, hydration with 0.45% saline 12 hr before and 12 hr after angiography provided better protection against renal function deterioration than did hydration with 0.45% saline plus mannitol or saline plus furosemide (CIN 11% vs. 28% vs. 40%; p=0.05).

CIN Consensus Working Panel recommends adequate intravenous volume expansion with isotonic crystalloid (1.0–1.5 mL/kg/hr) for 3 to 12 hr before the procedure and continued for 6 to 24 hr to prevent development of CIN in patients at risk [35]. Caution is needed in patients with chronic heart failure. They can profit more from optimal hemodynamic stabilization than excessive hydration.

Sodium Bicarbonate

A prospective, single-center randomized trial of 119 patients by Merten *et al*. [36] has suggested that the use of sodium bicarbonate hydration is superior to sodium chloride hydration. Rates of CIN were significantly lower in the sodium bicarbonate group (1.7%, $n = 1$) when compared with the sodium chloride

group (13.6%, *n* = 8) when both cohorts were administered 154 mEq/L of either solution. Merten *et al*. suggest that free-radical formation (which is promoted by an acidic environment) can be inhibited by increasing the pH of normal extracellular fluid, with the use of bicarbonate.

However, enthusiasm behind use of bicarbonate has gone in vein after recently published MEENA [37] trial; which assessed the efficacy of sodium bicarbonate in comparison to sodium chloride in patients of CIN. It concluded that although the incidence of dialysis was lower in patients receiving sodium bicarbonate but mortality was not significantly different in two groups. Sodium bicarbonate is no longer a standard recommended treatment for CIN.

N acetylcysteine

There is some evidence that reactive oxygen species have a role in renal damage caused by contrast agents [9]. *N* acetylcysteine (NAC), a thiol-containing antioxidant, is thought to act either as a free-radical scavenger or as a reactive sulfhydryl compound that increases the reducing capacity of the cell. It may also increase the biologic effects of NO by combining with NO to form *S*-nitrosothiol, which are a more stable form and a potent vasodilator. It also increases the expression of NO synthase and may thus also improve blood flow.

Earlier; Several subsequent studies confirmed the value of *N*-acetylcysteine in preventing contrast-induced nephropathy [38, 39]. Based on these data, *N*-acetylcysteine became widely accepted as a prophylactic therapy.

Lately, however, enthusiasm regarding the efficacy of acetylcysteine has been diminished, as several studies did not show a significant benefit of acetylcysteine in comparison to controls [40, 41]. For example; Durham *et al*. [40] studied 79 patients with chronic kidney disease who underwent diagnostic cardiac catheterization, percutaneous coronary intervention, or both. The patients were randomly assigned to receive oral acetylcysteine or placebo. All patients received hydration with 0.45% saline for up to 12 hours before and after catheterization. There was no significant difference in the incidence of contrast induced nephropathy between the two groups: 26.3% in the acetylcysteine group and 22% in the control group.

However, a recent *meta-analysis of 41 randomized trials* [42] that involved use of pharmacotherapy to the treatment group; found that preprocedural treatment with *N*-acetylcysteine was more effective in reducing the risk for CIN than the hydration alone.

These recent studies, coupled with the favorable side effect profile of NAC and its low cost, mean that NAC has gained favor in many centers as a preventive therapy, particularly in the high-risk group undergoing coronary interventions.

Dopamine

Given its dilatory effect on the renal vasculature and the ability to increase renal blood flow and GFR, dopamine was supposed to be useful in the prevention of CIN. This hypothesis was evaluated in several studies and the results turned out to be conflicting [43, 44]. Dopamine was shown to attenuate the increase in creatinine level after exposure to contrast media in one study [43], while in others; such effect was not documented at all. Moreover, in patients with peripheral vascular disease and CIN the effect of dopamine on renal function was found to be deleterious [44]. So use is no longer recommended.

Fenoldopam

Fenoldopam, a selective, dopamine-1 receptor agonist known to produce both systemic and renal arteriolar vasodilatation, was shown to blunt the decline in renal blood flow and GFR in animals exposed to contrast media. However; a prospective trial by Stone *et al*. [45] didn't find any beneficial effect with the use of fenoldopam. In this double-blind trial, a total of 315 patients (all treated with saline 0.45%) were randomized to fenoldopam (0.05 lg/kg/min titrated to 0.1 lg/ kg/min) or placebo starting 1 hr before the procedure and continuing for 12 hr afterward. There was no significant difference in the incidence of CIN within 96 hr in the 2 groups (33.6% vs. 30.1%, respectively; *p*=NS), or rates of dialysis, rehospitalization, and death at 30 days. Fenoldopam is, thus no longer recommended for CIN prophylaxis.

Theophylline

Adenosine is supposed to be key mediator involvement in the renal hemodynamic response to contrast media [46]. This raised the hypothesis that adenosine A1 receptor antagonist, theophylline, may attenuate the decrease in renal blood flow and GFR induced by the exposure to contrast media. The use of theophylline as a prophylactic agent for contrast-induced nephropathy was first assessed by Erley *et al*. [47] which was subsequently confirmed by Kapoor *et al*. [48]. Results of other randomized trials, however; lacked beneficial effect of theophylline compared with placebo in preventing CIN [44]. But, a recent meta-analysis of 9 randomized trials confirmed nephroprotective role of it [49]. So, in the wake of a lack of consensus in clinical studies, coupled with potential side effects of theophylline and the narrow therapeutic index of this drug, theophylline cannot yet be recommended for routine prophylactic use in the current clinical setting.

Atrial Natriuretic Peptide

Atrial natriuretic peptide in three different doses failed to prevent CIN in the randomized, placebo-controlled study of Kurnik *et al*. [50].

Diuretics

Study by Solomon *et al*. [19], revealed deleterious effects of diuretics furosemide and mannitol

Contrast media

Clinical Studies Comparing Low-Osmolar and High-Osmolar Contrast Media

With the introduction of low-osmolar and iso-osmolar contrast media, a reduction in the incidence of CIN has been observed [5, 14, 25-31]. Low-osmolar contrast media have gained widespread clinical acceptance because of fewer adverse effects than high-osmolar contrast media, particularly in high-risk patients [14,22, 23,25,26] It should be remembered, however, that several initial studies did not show significant differences in CIN between low-osmolar and high-osmolar contrast media. Finally, the prospective, randomized trial by Rudnick *et al*. [23] clearly demonstrated that patients with preexisting renal insufficiency alone or combined with diabetes mellitus had a significantly lower risk of CIN when low-osmolar contrast media are used. Subsequently, a meta-analysis of 25 trials with available data revealed a pooled odds ratio of CIN with low-osmolar contrast media of 0.61 (95% CI, 0.48 to 0.77) times that with high-osmolar contrast media. Furthermore, for patients with preexisting renal insufficiency, this odds ratio was 0.5 (95% CI, 0.36 to 0.68), whereas it was 0.75 (95% CI, 0.52 to 1.10) in patients without prior renal insufficiency [30].

Clinical Studies Comparing Iso-Osmolar and Low-Osmolar Contrast Media

Several studies have included both iso-osmolar and lowosmolar contrast media when investigating the incidence of CIN [27, 28]. Earlier, promising results were shown In NEPHRIC trial by Aspelin *et al*., [27] in which; the iso-osmolar contrast agent iodixanol was found to have significantly less incidence of CIN than the low-osmolar contrast agent iohexol in patients with diabetes mellitus and chronic renal failure (3.1% vs. 26.2%,respectively; relative risk, 0.12; 95% CI, 0.03 to 0.50; *P*=0.002).But it should be clear in mind that most of these trials, had limitations of small sample size, lack of proper study design, also benefits were seen only in high risk patients i.e. those with preexisting renal insufficiency, while in patients with normal renal function differences were not significant.

However; in recently published RECOVER [29], ICON [51] and CARE [52] trials, no significant difference, regarding occurrence of CIN or rise in SCr., was found between the two groups. In CARE trial [52], the incidence of CIN by any definition was not statistically different in the 2 study groups. The rate of absolute increases in SCr ≥0.5 mg/dL, was 4.4% in the iopamidol-370 group and in 6.7% in the iodixanol-320 group (CI, –6.7% to 2.1%; *P*=0.39). A relative≥25% increase in SCr occurred in 9.8% of the patients given iopamidol-370 and in 12.4% of the patients given iodixanol-320 (95% CI, –8.6% to 3.5%; *P*=0.44). In conclusion, it prudent to presume that the iso osmolar contrast media exhibit lower nephrotoxic properties more than the low osmolar media, until large prospective trials are conducted.

Hemodialysis and Hemofiltration

Study by Marenzi *et al*. [53] investigated the effect of continuous venovenous hemofiltration in prevention of CIN in patients with severe chronic renal insufficiency (serum creatinine >2 mg/dL) in comparison with intravenous hydration. Increase of creatinine >25% (5% vs. 50%, respectively; P < 0.001) and in hospital mortality (2% vs. 14%, respectively; P=0.02) were significantly lower in group with hemofiltration. Despite these impressive results, the conclusions of this study should be viewed with some caution. Removal of creatinine by hemofiltration per se could result in a lower incidence of contrast-induced nephropathy, although this alone would not account for differences in mortality. Moreover, the mortality rate in the control group was inordinately high, suggesting that it was not a good representative cohort.

CONCLUSION

Contrast-Nephropathy is an iatrogenic disorder, resulting from exposure to contrast media. Although rare in general population, CIN has a high incidence in patients with underlying renal disorder, diabetics and the elderly. Because CIN is a potentially serious yet avoidable adverse event, physicians using CM should incorporate preventive strategies into their clinical practices. The routine use of eGFR is strongly recommended as a method to identify the patient at risk for CIN. The best way to prevent CIN is to identify the patients at risk and to provide adequate periprocedural hydration. The role of various drugs in prevention of CIN is still controversial and warrants future studies. Despite remaining uncertainty regarding the degree of nephrotoxicity produced by various contrast agents, in current practice nonionic low-osmolar contrast media are preferred over the high-osmolar contrast media in patients with renal impairment.

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