Review

Contrast nephropathy in children

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Abstract. Contrast-induced nephropathy (CIN) remains a common and potentially serious complication in at risk patients after exposure to contrast agents. Risk factors for CIN include chronic kidney disease, hypotension, diabetes mellitus, recent previous exposure to contrast and all of these are potentially additive. Therefore, careful pre-procedural risk stratification is important. In high-risk patients, contrast should be avoided if possible. If avoidance is not possible, the volume of contrast should be minimized and the type of contrast used should if possible be non-ionic iso-osmolar contrast. In view of the clinical importance of CIN, numerous potential risk-reduction strategies have been evaluated. Adequate intravenous volume expansion with isotonic crystalloid (1.0–1.5 mL/kg per hr) for 3–12 hr before the procedure and continued for 6–24 hr afterward can lessen the probability of CIN in patients at risk. But there are insufficient data on oral fluids as a preventive strategy. Nephrotoxic drugs should be withdrawn before contrast administration in patients at risk for CIN. No adjunctive medical or mechanical treatment has been proved to be efficacious in reducing risk for CIN including prophylactic hemodialysis and hemofiltration, N-acetylcysteine, fenoldopam, dopamine, calcium channel blockers, atrial natriuretic peptide, and L-arginine. The CIN Consensus Working Panel considered that, of the pharmacologic agents that have been evaluated, theophylline, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), ascorbic acid, and prostaglandin E deserve further evaluation.

Keywords: Contrast-induced nephropathy, acute kidney injury, acute renal failure

1. Introduction

The definition of contrast-induced nephropathy (CIN) varies but broadly is a term used to describe an increase in serum creatinine or a reduction in renal function (acute kidney injury (AKI) observed within the first 24 hr after contrast exposure and peaking up to 5 days afterwards [1]. Due to a lack of a consensus definition of pediatric AKI, papers vary in their definition of an “increase in serum creatinine” with some using an absolute increase in mg/dL and others utilizing a proportional rise of 25–50% above baseline. In preparing of this review article, there are several issues, which limit the quality of any review article on CIN;

published reports vary considerably in patient population, types of procedures performed, types of contrast used and definitions of renal dysfunction. In addition, many publications were quite outdated and finally pediatric papers on CIN were rare and inadequately powered when available. Utilizing available literature, we attempt to concisely summarize and describe the current state of CIN in children.

2. Incidence

The precise incidence and prevalence of pediatric AKI are not known and the incidence and underlying etiology varies globally. With improved availability of anti-infectives, in developed countries, the etiology of pediatric AKI has shifted from primary glomerular diseases to hospital-acquired causes of renal disease. This includes exposure to nephrotoxins such as contrast [2]. The possible beneficial effect of increased awareness

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and risk prevention of CIN has been tempered by an ever-increasing dependence on contrast-inclusive radiologic procedures. Contrast media is being used in as many as 45 million patients undergoing computed tomography (CT) per year in the USA. Recently the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function and end stage renal disease (RIFLE) criteria have been regarded as a more sensitive tool for detecting AKI [3]. Using the RIFLE classification applied for the diagnosis of CIN, the incidence was 18.75% in 80 children undergoing cardiac angiography [4]; another study reported an incidence of 15% after intravenous urographic studies [5]. In children undergoing CT with contrast, rates are unclear but are thought to be very low if they have no other risk factors. In adults, CIN has been reported as the third most common cause of hospital-acquired renal failure and was responsible for 11% of the cases [6].

3. Pathophysiology

Our understanding of the pathophysiology of CIN remains incomplete. Contrast used for radiologic procedures are tri-iodinated benzene derivatives that rely on iodine for their radio-opacity. Iodinated contrast medium may be either ionic or non-ionic. The ionic type tends to create a high osmolality in blood and historically, contrast materials are classified by their osmolality. High osmolar contrast material is hyperosmolar to the plasma and is associated with red blood cell deformation, systemic vasodilation with consequent intrarenal vasoconstriction and direct tubular toxicity. Low osmolar contrast is still hyperosmolar to the plasma but less so. Iso-osmolar contrast has now been developed.

Pivotal to the pathophysiology of CIN is renal medullary hypoxia, pre-glomerular vasoconstriction and the cytotoxic effects of the contrast material itself, which is aggravated by the osmolality and viscosity of the contrast [7]. Contrast causes the release of renal vasoconstrictors such as adenosine and endothelin, which results in a reduction in medullary blood flow leading to medullary hypoxia and tubular cell death. In addition, the concentration of iodinated contrast in the renal tubules and collecting ducts allows for direct cellular injury and death to the tubular cells. Since the degree of cytotoxicity is related to length of exposure, high urinary flow rates during and after contrast procedures is essential. It is therefore clear that hypotension and superimposed issues such as bleeding

etc. can aggravate renal damage secondary to contrast. While the reduction of the osmolality of the contrast material has been greatly beneficial in preventing direct renal tubular hyperosmolar injury, it has come at the price of increased viscosity. The increased viscosity of the contrast reduces glomerular filtration rate (GFR) and medullary oxygenation with a consequent slowing of urinary flow leading to renal retention of contrast with subsequent aggravation of its cytotoxic effects [6]. Therefore, despite our progress and efforts to reduce CIN, currently there is no available contrast material without clinical nephrotoxicity although the degree and extent of cellular toxicity may vary from contrast to contrast. There are studies suggesting that in high-risk patients (defined below), iso-osmolar contrasts may be less likely to induce CIN than low-osmolar contrast [8]. Similarly, non-ionic contrast media are less likely to induce CIN [9].

4. Risk factors

Chronic kidney disease and concurrent AKI are known risk factors for the development of CIN [10]. Hypotension and volume depletion increases the risk of CIN, likely due to the increased risk of renal ischemia and urinary stasis increasing contrast transit time through the renal tubules. This is particularly relevant in the acutely ill children in the intensive care unit setting frequently requiring radiologic studies with contrast. Repeated exposure to iodinated contrast over a period of a few days, although not proven, is presumed to be a risk factor for CIN and is to be avoided.

Although diabetes mellitus in adults has not been shown to be necessary for the development of CIN, it does appear to act as a risk multiplier in patients with chronic kidney disease. But many of these studies were done using hyperosmolar contrast which is almost never utilized now [11].

Contrast exposure in angiography, carries an increased risk of CIN, as do patients requiring non-elective contrast enhanced CT scans. A possible reason for the higher incidence of AKI in an emergency setting may be that these patients are more likely to have comorbidities that were not adjusted for, such as hypotension, hyperglycemia, or volume depletion.

Risk of CIN in pediatric kidney transplant recipients has not been elucidated but it is reasonable to presume that they are at higher risk than non-transplant recipients and clinicians should be conservative in ordering imaging studies utilizing contrast.

5. Clinical features and management

The onset of kidney injury is probably within minutes of exposure to contrast agents, however the increase in the serum creatinine may take a day or two to develop. Most patients are nonoliguric. Almost all cases are mild with a decline in serum creatinine within three to seven days. Other manifestations of AKI including hyperkalemia, acidosis, and hyperphosphatemia may occur. The urinary sediment may show classic findings of acute tubular necrosis, including muddy brown granular and epithelial cell casts and free renal tubular epithelial cells without evidence of glomerular disease (such as dysmorphic red blood cells or red blood casts) or interstitial nephritis (such as white cells or white cell casts). Many of the commonly used iodinated radiocontrast agents induce false positive results on dipstick or sulfosalicylic acid testing for proteinuria. Therefore, urine should not be tested for protein for at least 24 hr after a contrast study. The fractional sodium excretion (FENa) is often <1% in patients with CIN. There are no characteristic radiographic features of CIN. A prolonged nephrogram may be seen among patients with established CIN who undergo a contrast enhanced CT scan.

Most cases of CIN are self-limited. Management is conservative as with any other case of AKI. Dialysis is indicated in an estimated 1% of cases of CIN [12]. In patients with underlying renal impairment, the frequency of dialysis in CIN may be as high as 4% [13]. Although rarely indicated, the impact of dialysis on patient prognosis and mortality is considerable.

There is an often ignored increased risk of death in adult patients with CIN with reported mortality rates as high as 20% [14]. In a large, retrospective hospital-based study, after adjusting for co-morbid disease, patients with CIN had a 5.5-fold increased risk of death [15]. The development of CIN has also been associated with an increased hospital stay [16] thereby increasing the economic burden of the admission [17].

6. Prevention strategies

Progress in the development of strategies to prevent CIN has been hindered by the lack of consensus definition and an inability to accurately define high-risk children. In pediatrics in particular, the insensitivity of creatinine as a marker for renal function is well known since it varies widely with age, gender,

muscle mass/metabolism, medications and hydration status. There has to be considerable loss of kidney function before the serum creatinine changes. In addition, the serum creatinine does not accurately depict kidney function until steady-state equilibrium, which can take several days. Neutrophil gelatinase-associated lipocalin (NGAL) in urine and plasma, 2 hr after contrast administration have been shown to be predictive biomarkers of CIN [18] but these results remain unvalidated [19]. Biomarkers such as NGAL could allow for earlier identification and intervention to avoid bad outcomes associated with CIN.

Several prevention strategies have been suggested and studied with varying outcomes, but first and foremost, identifying risk factors in children undergoing contrast-inclusive procedures is essential to allow for appropriate preventive strategies and surveillance for CIN. Since it can be agreed that AKI and CKD are risk factors for the development of CIN, it is important to assess renal function before administration of contrast. Serum creatinine and estimated GFR should be assessed [20] and in emergency situations whenever possible, parents should be thoroughly questioned to obtain an indication of whether the child has impaired renal function that could increase the risk of AKI on exposure to contrast. A thorough history is also essential to rule out other risk factors such as diabetes mellitus, volume depletion, concurrent nephrotoxic drugs including but not limited to non-steroidal anti-inflammatory agents, hemodynamic instability and other co-morbidities. Appropriate initial measures include cessation of nephrotoxic drugs and avoidance of contrast if possible. Other strategies to reduce risk are detailed below.

6.1. Lower contrast volumes

Contrast volume is an independent predictor of the development of CIN [12]. The volume of contrast should be determined by the size of the child, the study being performed and the estimated GFR [21].

6.2. Osmolarity and binding of contrast utilized

Over the past four decades, osmolalities of available contrast agents have been gradually decreased to physiologic levels. High osmolar contrast is almost never used and are therefore not discussed in this review. Most studies done to ascertain which of the low-osmolar contrasts were best were weakly powered

single center studies. As per the CIN consensus working panel report, iodixanol is the least nephrotoxic low osmolar agent available [22]. But in low risk patients this benefit was not evident and iodixanol had a similar risk profile to other low osmolar contrast agents [22]. In patients on dialysis, National Kidney Foundation - Kidney Disease Outcomes Quality Initiative recommends the use of iso-osmolar contrast agents to reduce the chances of volume overload [23].

The iodine in the contrast may be bound either in an organic (non-ionic) compound or an ionic compound. Non-ionic contrast, which covalently binds the iodine, was thought to have fewer side effects as they do not dissociate into component molecules. But in high-risk patients undergoing coronary angiographic procedures, use of the nonionic iso-osmolar iodixanol did not reduce renal deterioration in patients with renal impairment, compared with the ionic low-osmolar ioxaglate [24].

6.3. Volume expansion

The administration of intravenous fluid remains the cornerstone prevention of CIN. Studies have shown that good urine output in the 6 hr after contrast exposure is associated with reduced AKI [25] since it likely reduces the concentration of contrast media in the tubule and expedites excretion of the contrast. However, no well-defined protocols exist to guide type, quantity and duration of fluid administration with only a few studies directly addressing this theme. The most commonly utilized fluid is isotonic saline, which has been shown to perhaps be superior to half-isotonic saline [26]. This effect was even more pronounced in diabetics [27].

Since alkalization may protect against free radical injury, randomized trials and meta-analyses have studied sodium bicarbonate infusions for the prevention of CIN. The results are conflicting due to the significant heterogeneity in the studies. In general, isotonic sodium bicarbonate versus isotonic sodium chloride is associated with equivalent or better outcomes [27–30]. Unfortunately, isotonic sodium bicarbonate is not commercially available. Concern for potential harm from errors in compounding bicarbonate solutions at point of care or in the hospital pharmacy could be a reason to utilize isotonic saline instead.

Therefore although the optimal type of fluid and timing of administration are not well established, if there are no contraindications to volume expansion,

isotonic normal saline prior to and continued for several hours after contrast administration in high risk patients with the capacity to handle the fluid volume is advisable. Many papers suggest rate of administration to be 1 mL/kg/hr for 12 hr before and 12 hr after contrast administration [31].

Given that an increasing number of individuals receive contrast as outpatients, small trials have been done to evaluate the effectiveness of oral hydration in preventing CIN but no conclusive recommendations can be made due to the heterogeneity and small size of the studies [32–34].

Since CIN is a frequent complication of coronary diagnostic and interventional procedures in patients with CKD, preventive intravenous hydration must be done cautiously to avoid over hydration and pulmonary edema especially in patients with left ventricular dysfunction. Therefore, in adults undergoing coronary angiography, two methods have been used to guide fluid repletion. The first is utilizing the left ventricular (LV) end-diastolic pressure to guide the rate and quantity of fluid administration. In a recently published randomized trial done in 350 adults, contrast-induced AKI (defined as >0.5 mg/dL or $>25\%$ increase in serum creatinine between 1 and 4 days after the procedure) occurred less frequently in the LV end-diastolic pressure group, compared with control. But even in the LV end-diastolic pressure guided group, three patients stopped intravenous fluids early because of dyspnea [35]. A larger study is needed to confirm these findings but this is not generalizable to all children receiving contrast and is of relevance only in cardiac patients. The second method utilized in this population to guide fluid administration was the renal guard system, which is an extra-corporeal circuit for fluid infusion to match the volume of urine output, which can be forced by diuretic administration. Although preliminary results are promising, this has not been evaluated in children and additional studies that address the possible electrolyte issues etc. are necessary before forced diuresis and matched volume replacement are used clinically [36].

6.4. Pharmacologic strategies

Worldwide there are no approved drugs for the prevention of CIN. Drugs that have been assessed include vasodilators, intrarenal mediator antagonists and cytoprotective agents. Some relevant agents are discussed below.

6.4.1. *N-acetylcysteine (NAC)*

Assuming that reactive oxygen radicals may be involved in the pathogenesis CIN, anti-oxidant NAC has been used to protect against CIN. Although earlier studies suggested a beneficial effect [37] subsequent meta-analysis suggest otherwise. NAC causes a decrease in serum creatinine without affecting GFR possibly due to increased tubular secretion or increased muscle metabolism, which makes its effect on CIN difficult to determine [38]. Based on the available literature, NAC is not indicated for CIN prevention.

6.4.2. *Adenosine antagonists*

Theophylline/aminophylline have been evaluated in 11 studies including nine randomized controlled tri-

als and while some showed a reduction in risk others did not. A meta-analysis of 480 patients in seven trials showed a statistically significant effect on the decline in renal function after contrast administration [39]. The CIN consensus working panel suggested further studies to validate the potential benefits versus the potential for serious side effects. Its role in pediatrics remains undetermined.

6.4.3. *Fenoldopam*

A selective dopamine A1 receptor agonist, fenoldopam is a renal vasodilator. It was hoped that this drug would be protective as shown in initial small-uncontrolled studies [40]. Unfortunately, this was not proven in larger trials [41].

Table 1
Summary of contrast nephropathy in children

Risk factors
Pre-existing acute kidney injury
Chronic kidney disease
Hypotension
Volume depletion
Diabetes mellitus
Contrast exposure in angiography and non-elective computed tomography
Preventive strategies
Stratify and identify high-risk patients
Check patients for above risk factors
Assess renal function before contrast administration
In emergency situations where eGFR cannot be determined prior to contrast exposure, parents should be thoroughly questioned for evidence of impaired renal function as well for other risk factors
Avoid contrast if possible particularly in high-risk patients
Avoid repeated exposure to contrast over a period of a few days
Discontinue nephrotoxic drugs including non-steroidal inflammatory drugs
Minimize contrast volume based on eGFR and size of child
Utilize iso-osmolar contrast wherever possible particularly in dialysis patients
Optimize patients hydration status (various fluid rates and types are described in text) to ensure good urine output for at least 6 hr following contrast exposure*
There are currently no approved adjunctive pharmacologic or mechanical treatment for contrast nephropathy
Clinical features
Increased serum creatinine within 1-2 days of contrast exposure
Usually non-oliguric
Features of acute kidney injury (hyperkalemia, hyperphosphatemia, acidosis, azotemia etc.)
Bland urinary sediment with/without muddy brown granular casts, sterile pyuria
False positive protein dipstick
Fractional excretion of sodium <1%
Prolonged nephrogram
Treatment
Conservative management of acute kidney injury
Strict input and output assessments of patients with daily weight for optimal fluid control
Fluid restriction if evidence of fluid overload
Vigilant monitoring of electrolytes
Potassium, protein and phosphorous restriction depending on laboratory investigations
Renal dosing of all medications based on eGFR
Cessation and avoidance of nephrotoxins

eGFR = Estimated glomerular filtration rate. *The literature is varied on type and duration of intravenous fluids recommended to prevent contrast nephropathy. In patients with normal kidney and heart function, we would suggest normal saline as fluid of choice. Many papers suggest rate of administration to be 1 mL/kg/hr for 12 hr before and 12 hr after contrast administration (Please see text for details).

6.4.4. Alpha-2-receptor agonists

Clonidine and dexmedetomidine have been shown in mice to protect against CIN presumably by decreasing regional vascular resistance with increased medullary blood flow [42]. In a randomized prospective double-blinded study of 60 children undergoing cardiac angiography, CIN occurred in only 10% of children who received dexmedetomidine compared to 37% of the controls [19]. The beneficial effect of dexmedetomidine may be due to its preventive effect on the release of vasoconstrictor agents such as endothelin and renin but since this study was restricted to low-risk patients, the results cannot be generalized.

6.4.5. Miscellaneous drugs

Calcium channel blockers [43], L-arginine [44] and atrial natriuretic peptide [45, 46] have all been studied in adults and have not shown consistent benefit in the prevention of CIN. Statins have been proposed to reduce CIN due to their beneficial effects on endothelial function and reduction in oxidative stress [47–49] but their role in pediatric patients in whom these drugs are not otherwise indicated is limited. Ascorbic acid is an anti-oxidant that has been shown in a randomized double-blinded placebo controlled trial of 231 patients to reduce CIN but the study was limited to adults undergoing cardiac catheterization and since it has poor bioavailability after oral administration, it would require intravenous administration [50]. Subsequent studies have had conflicting results [51–53]. Since renal vasoconstriction is a critical component of CIN pathogenesis, prostaglandin E1 deserves further evaluation based on initial pilot study results [54].

6.5. Prophylactic hemodialysis or hemofiltration

In 114 consecutive adult patients with CKD in an Italian center, hemofiltration for 4–6 hr before and 18–24 hr after coronary angiography or elective percutaneous coronary intervention resulted in a reduction in CIN (5% vs. 50%; $P < 0.001$) and emergency hemodialysis (0% vs. 18%) compared to the control group that received normal saline hydration [55]. On the contrary, although dialysis is effective in removing contrast medium, prophylactic hemodialysis for 3 hr initiated immediately following contrast exposure did not show any beneficial effect compared to saline hydration alone. In fact, patients treated with prophylactic hemodialysis were more likely to have a decline in renal function and require additional hemodialysis

[56]. Hemodialysis can be associated with hypotension, which could potentially worsen renal ischemic injury. Hemofiltration is associated with hemodynamic stability and does remove the contrast from the circulation. But the beneficial results of hemofiltration have not been validated. In addition, it may not be applicable to children with less risk factors and co-morbidities undergoing procedures requiring less contrast particularly since it is cost-ineffective and requires an intensive care unit setting.

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