www.nephropathol.com DOI: 10.12860/jnp.2014.12 J Nephropathol. 2014; 3(2): 51-56

Journal of Nephropathology

Contrast-induced nephropathy; A literature review

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ARTICLE INFO

Article type:
Short-Review

Article history:
Received: 17 December 2013
Revised: 4 January 2014
Accepted: 18 January 2014
Published online: 1 April 2014
DOI: 10.12860/jnp.2014.12

Keywords:
Contrast-induced nephropathy
Contrast media
Percutaneous coronary intervention

ABSTRACT

Context: Contrast–induced nephropathy (CIN) is a common cause of acute kidney dysfunction.

Evidence Acquisitions: Directory of Open Access Journals, Google Scholar, PubMed, EBSCO and Web of Science have been searched.

Results: It is necessary to identify at risk patients at early stages to implement preventive strategies to decrease the incidence of this nephropathy. However, mechanisms of CIN have not fully explained yet. It seems that mechanisms which mediated by nitric oxide and prostaglandin-induced vasodilatation have been played a crucial role in the CIN. Hemodynamic changes of renal blood flow, which causes hypoxia in the renal medulla and direct toxic effects of contrast media on renal cells, are thought to contribute to the pathogenesis of CIN. Contrast media is normally divided into iso-osmolar, low-osmolar, and high-osmolar. N-acetylcysteine is considered as one of the best choices to prevent CIN in high-risk groups.

Conclusions: The first aim to prevent CIN is identifying high-risk subjects and controlling associate risk factors. As significant differences existed between contrasts agents due to their physicochemical properties, low-osmolar or iso-osmolar contrast media should be used to prevent CIN in at-risk patients. The volume of contrast media should be as low as possible.

Short-Review

Implication for health policy/practice/research/medical education:
Contrast-induced nephropathy is a common cause of acute renal functional impairment and accounts for significant morbidity and mortality. The primary goal should be avoiding contrast media to prevent contrast-induced nephropathy, if at all possible, and risk factors should be recognized. As significant differences between contrast agents due to their physicochemical properties exist, low-osmolar or iso-osmolar contrast media should be used to prevent contrast-induced nephropathy in at-risk patients. The volume of contrast media should be as low as possible.

Please cite this paper as: Golshahi J, Nasri H. Gharipour M. Contrast-induced nephropathy; A literature review. J Nephropathol. 2014; 3(2): 51-56. DOI: 10.12860/jnp.2014.12

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1. Context

Contrast media-induced nephropathy (CIN) is considered as a common cause of acute kidney dysfunction after percutaneous coronary intervention (1).

2. Evidence acquisition

Directory of Open Access Journals, Google Scholar, PubMed, and Web of Science were searched with keywords relevant to contrast-induced nephropathy, contrast media, percutaneous coronary intervention.

3. Results

Forty original and review articles relevant to this topic directly or indirectly were found. From the information given in these papers, we attempt to discuss about six major concerns of CIN, important in clinical practice: 1) clinical aspects, 2) prevalence of CIN, 3) pathophysiology, 4) contrast agents and renal cell apoptosis, 5) relationship between CIN and different contrast media, 6) prevention of CIN by drugs and procedures.

3.1. Clinical aspects

CIN is one of the most important post-operative adverse events after cardiac procedures.

The definition of CIN comprises absolute (≥ 0.5 mg/dl) or relative increase (≥ 25%) in serum creatinine value at 48-72 h after exposure to a contrast agent compared to baseline serum creatinine values, while alternative explanations for renal impairment have been excluded (1-3). CIN is often undetected clinically because patients are asymptomatic. Contrast media have serious toxic implication on kidney tubular cells (2). CIN is the third most usual cause of hospital-acquired acute renal failure after impaired renal perfusion and nephrotoxic treatments. Several definitions regarding CIN in subjects who have undergone cardiac interventions has been defined. Recently suggested definition by Harjai, *et al.* (3) categorized, contrast nephropathy as grade 0 (serum creatinine increase <25% above baseline and <0.5 mg/dL above baseline), grade 1 (serum creatinine increase ≥25% above baseline and <0.5 mg/dL above baseline), or grade 2 (serum creatinine increase ≥0.5 mg/dL above baseline).

3.2. Incidence of CIN

The incidence of CIN has been calculated to be >2% in the general population but in high-risk patients, i.e., diabetic patients, subjects with history of congestive heart failure, chronic renal impairment, and older age, the incidence has been considered to be >20% to 30% (4). Almost the rate of CIN is about 150000 patients each year in the world, and at least 1% requires dialysis and a prolonged hospital stay (5). Rudnick *et al.* (6) reported that patients with history of kidney failure alone or combined with diabetes mellitus had a notably lower risk of CIN when low-osmolar contrast media are used. It is well-documented that, CIN increases the length of hospital stay cost and medical treatment and morbidity (7).

Several risk factors have been described for CIN. Mehran *et al.* have reported a risk score for prediction of CIN after percutaneous coronary intervention (8). Their suggested risk scores include hypotension (5 points, if systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive heart failure (5 points, if class III/IV by New York Heart Association classification or history of pulmonary edema), age (4 points, if >75 years), anemia (3 points, if hematocrit <39% for men and <36% for women), diabetes mellitus (3 points), contrast media volume (1 point per 100 mL), estimated glomerular filtration rate (eGFR); 2 points, if eGFR 60 to 40; 4 points, if eGFR 40 to 20; 6 points, if eGFR <20. A risk score of >6, 6 to 10, 11 to 16, and >16 indicates a risk for CIN of 7.5%, 14%, 26%, and 57%, respectively. It is well-documented that, risk of CIN increases by higher contrast volume (9-12), additionally, Sadeghi *et al.* showed that the use of high dose of contrast agent was strongly related to the incidence of acute

kidney failure when it is combined with cardiac surgery (13). It seems that raising the rate of CIN is due to increasing the number of angiographies and CT examinations in clinical practice as well as administered higher doses of contrast media to sicker and older patients (14-16).

3.3. Pathophysiology

The precise mechanisms of CIN have not been explained in details. It has been observed that, adenosine, endothelin, and free radical-induced vasoconstriction increase following CIN while nitric oxide and prostaglandin-induced vasodilatation decrease, then ischemia in the deeper portion of the outer medulla will occur. Furthermore, contrast agents have direct toxic effects on kidney tubular cells, inducing vacuolization, change in mitochondrial function, and even apoptosis (17,18).

3.4. Risk Factors

Various, strategies are available to decrease the likelihood that patients will experience CIN. Diabetes mellitus (type 1 and type 2) and impaired kidney function are considered as important risk factors for CIN. In high risk patients different levels of GFR can be considered as a risk factor too. The highest risk is associated with GFR of less than 30 mL/min; the lowest risk, with GFR levels of 60 mL/min or greater, except for patients with diabetes (19). Additionally diabetic subjects with normal GFR have increased risk of CIN because of endothelial dysfunction of the renal vessels, resulting in suppressed tonic influence of nitric oxide (20).

3.5. Contrast agents and renal cell apoptosis

Several factors have thought to be related to pathogenesis of CIN, for example hemodynamic changes of renal blood flow, which causes hypoxia in the renal medulla, direct toxic effect of the contrast media on renal cells (21). Both clinical trials and animal experiments showed predominant toxic effect of contrast media on renal tubules. In addition, administration of compounds with antioxidant properties [such as N-acetylcysteine, ascorbic acid, and sodium bicarbonate] has found as an effective strategy to prevent CIN (22-24). Romano *et al.* demonstrated the apoptotic effect of the iso-osmolar and low-osmolar contrast media on human embryonic kidney, porcine proximal renal tubular, and canine Madin–Darby distal tubular renal, cells (25,26). Recently it has shown that, sodium bicarbonate and ascorbic acid had acceptable properties to avoid CIN (27), notably, Romano *et al.* showed that ascorbic acid has lower effect against contrast-induced apoptosis than NAC. In contrast, sodium bicarbonate does not prevent contrast-induced apoptosis. Additionally, newly clinical studies suggest that the sodium bicarbonate seems to be effective in preventing CIN (28). It has been assumed that alkalinizing renal tubular fluid with bicarbonate could decrease injury (29-31).

3.6. Relationship between CIN and different contrast media

For the first time at 1968, Almén et al. suggested about low-toxicity, nonionic, monomeric and dimeric contrast media, and since then, others proposed about the attribution of osmolality, viscosity, and chemotoxicity on the toxicity of different contrast media (32).

Today, contrast media are commonly divided into high-osmolar, low-osmolar, and iso-osmolar agents. The osmolality value is often stated in terms of the ratio between the number of iodine atoms and the number of dissolved particles (32). Low-osmolar contrast media have gained widespread clinical acceptance because of fewer adverse effects than high-osmolar contrast media, particularly in high-risk patients with an elevated pre-procedural serum creatinine (33).

3.7. Prevention of CIN

Studies suggest that intravenous hydration is the most effective strategy to prevent CIN (34). Hydration is inexpensive and is usually risk-free. The volume of contrast media and the frequency of administration should be minimized, to

ensure satisfactory image quality. Liberal salt and oral fluid intake or avoidance of fluid restriction may be recommended for patients at low to moderate risk for CIN (34). Sodium bicarbonate and N-acetylcysteine are considered as two strategies which are recommended to prevent an acidic environment and formation of free radicals in the renal tubules (35). N-acetylcysteine increases production of nitric oxide, which has vasodilatory capabilities, and the concentration of glutathione, which acts as a free radical scavenger. Compared with infusion of normal saline alone, administration of N-acetylcysteine in conjunction with infusions of normal saline significantly decreased the risk for CIN (36). Published results showed that N-acetylcysteine has gained favor in clinical practice as a preventive therapy in high-risk groups, like in patients with preexisting renal failure (37). Several prospective, randomized clinical trials showed that the administration of N-acetylcysteine along with hydration significantly decreased CIN in high-risk patients (37). Briguori et al. (36) highlighted the effect of N-acetylcysteine dosage. In addition, Baker et al. (38) demonstrated that, the intravenous administration of high-dose N-acetylcysteine was also effective. Ascorbic acid, theophylline, fenoldopam, and calcium antagonists, and periprocedural hemofiltration have been recommended to prevent CIN too (39). Periprocedural hemofiltration is an invasive and costly procedure, which is not confirmed by evidences yet. This procedure is not directly applicable to all high-risk patients who are exposed to contrast agents for simpler procedures (40).

4. Conclusions

In summary, CIN is a common cause of acute kidney functional impairment and accounts for significant morbidity and mortality. The primary goal should be avoided contrast media to prevent CIN, if at all possible, and risk factors should be recognized. As significant differences between contrasts agents due to their physicochemical properties exist, and low-osmolar or iso-osmolar contrast media should be used to prevent CIN in at-risk patients. The volume of contrast media should be as low as possible.

Authors' contributions

All authors wrote the manuscript equally.

Conflict of interest

The author declared no competing interests.

Funding/Support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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