Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2020, 9(1)99-104

Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Evaluation of Contrast-Induced Acute Kidney Injury (CI-AKI): A Literature Review

Yazeed Ahmed Turkistani[1*], Tariq Mohammed Alshami[1], Saleh Jameel Almatrafi[2], Adel Oudah Alahmadi[3], Safiah Ali Hashem Al Edrisy[4], Ghofran Yaslam Bazuhair[5], Fatimah Husni Ahmed Rajab[5], Abdullah Hussain A Alqawain[6], Bakr Akram S Jalawi[7], Shatha Abdullah Hashem[8], Hussam Jameel Khinkar[9], Aya Kamil Alkhudhairy[10]

[1] Department of Medical Science, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[2] Department of Medical Science, Faculty of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia
[3] Department of Medical Science, Faculty of Medicine, King Saud Bin Abdulaziz University For Health Science, Riyadh, Saudi Arabia,
[4] Department of Medical Science, Faculty of Medicine, Hashemite University, Amman, Jordan
[5] Department of Medical Science, Faculty of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia
[6] Department of Medical Science, Faculty of Medicine, Medical University of Warsaw, Warszawa, Poland
[7] Department of Medical Science, Faculty of Medicine, Jordan University, Amman, Jordan
[8] Department of Medical Science, Faculty of Medicine, Jazan University, Jazan, Saudi Arabia
[9] Department of Medical Science, Faculty of Medicine, Umm Al Qura University, Makkah, Saudi Arabia.
[10] Department of Medical Science, Faculty of Medicine, Alfaisal university, Riyadh, Saudi Arabia

***Email:** zedturk14 @ gmail.com*

ABSTRACT

Background: *The risk of contrast-induced acute kidney injury (CI-AKI) has been accepted lately by medical literature and practice since it is the third leading cause of acute kidney injury in hospitalized patients. Different measures in practice are being used to prevent the incidence of CI-AKI.* ***Objective:*** *In this review, we aimed to discuss the different methods of prevention of CI-AKI mentioned in the literature.* ***Methods:*** *A comprehensive search was done using biomedical databases including Medline, and PubMed, for studies concerned with the assessment of Contrast-Induced Acute Kidney Injury. Keywords used in our search through the databases were "Contrast-Induced Kidney Failure" and "Diagnosis & Management".* ***Conclusion:*** *Intravenous (IV) fluid hydration is the mainstay of practice in the prevention of CI-AKI. Intravenous administration of sodium bicarbonate has also gained notable importance in the prevention of CI-AKI, but it is still not confirmed. Despite that the application of N-acetyl cysteine to prevent CI-AKI is controversial, N-acetyl cysteine remains a commonly utilized agent even without solid scientific evidence. The application of statins for the prevention of CI-AKI after intravascular contrast medium administration revealed some promising results but it is still premature to implement their application in daily clinical practice. Therefore, there is a need for additional well designed and sufficiently powered randomized controlled trials to clarify these issues and to assess the risk vs benefit of all other methods for the purpose of CI-AKI prevention.*

Key words: *Contrast, Acute Kidney Injury, Diagnosis.*

INTRODUCTION

Kidney diseases are common health problems around the world and have different causes [1]. CI-AKI is described as a sudden impairment of renal function after the administration of iodinated contrast media, without the occurrence of other causes [2]. Lately, the risk of CI-AKI has been accepted extensively by medical literature and practice since the majority of investigations found a significant risk of intra-arterial and intravenous administration of contrast material [3, 4].

Based on Hou et al. [5], CI-AKI is the third leading cause of acute kidney injury in hospitalized patients. Appropriate risk stratification is the cornerstone of prevention of CI-AKI and the physician should be familiar with modifiable and non-modifiable risk factors and with how to suspect and diagnose a case of CI-AKI. Additionally, the various management options of CI-AKI are still controversial. In this review, we aimed to discuss the different aspects of CI-AKI mentioned in the literature.

METHODOLOGY

We carried out a comprehensive search utilizing biomedical databases including Medline, and PubMed for studies concerned with CI-AKI published in the English language. Keywords used in our search through the databases were "Contrast-Induced Kidney Failure" and "Diagnosis & Management". More relevant articles were recruited from references lists scanning of each included study.

DISCUSSION

CI-AKI is described by The European Society of Urogenital Radiology as an impairment in renal function, with >0.5 mg/dl or >25% enhancement in serum creatinine within 3 days after intravascular administration of the contrast material, in the lack of an alternative etiology [6]. Several descriptions of CI-AKI are reported in the literature. They mostly comprise of either a relative (25–100%) or absolute (0.3–1.0 mg/dL) rise in serum creatinine above baseline levels. In several laboratories, a modification of 0.3 mg/dL is not considered statistically significant. The most prevalent definition utilized is either a relative enhancement in serum creatinine from the baseline value of 25% or an absolute enhancement of 0.5 mg/dL within the first 2 days following contrast administration. In addition, the impairment of renal function must not be caused by other causes, and the creatinine must stay high for 2 to 5 days. Another definition for CI-AKI can be used which is oliguria when the urine output is less than 0.5 mL/kg/h for over 6 hours. However, urine output is not of that clinical sensitivity as patients may maintain urine output even in cases of a significant renal insult, especially if they were hydrated properly. Anyway, the development of oliguria is mostly correlated with a significant increase in serum creatinine, which is considered the definition of CI-AKI [7, 8].

The incidence of CI-AKI is reportedly high, worldwide [9, 10]. Between 4.6% and 16.4% of patients undergoing computed tomography (CT) scans or angiography developed CI-AKI in Sub-Saharan Africa, depending on the definition used [11]. In India, similar incidences of CI-AKI induced by intravenous administration of contrast media have been reported among patients (10%) and among pediatric patients undergoing CT scans in Germany (10.3%) [12-14].

Pathophysiology

Regarding pathophysiology, the main mechanisms which are thought to be responsible for CI-AKI are a complex interplay of direct toxic effects on tubular cells along with poor renal perfusion. Exposure of a nearly hypoxic renal medulla to a highly viscous contrast can increase vascular resistance. This will lead to reduced blood flow and hypoxic injury [15]. This, in turn, causes cytotoxic injury to the renal tubular cells. Production of reactive oxygen species, adenosine, and endothelin results in further renal vasoconstriction and inflammatory response causing direct toxicity to the kidney [16].

Risk Factors

The risk factors can be divided into modifiable and non-modifiable risk factors. Modifiable factors are the volume of contrast media, sepsis, anemia, dehydration, and nephrotoxic medications. Non-modifiable risk factors are age, diabetes, pre-existing renal disease, and congestive cardiac failure. The presence of pre-existing renal dysfunction is the most important risk factor for CI-AKI. According to Stevens et al. [17], an extremely low risk of developing

CI-AKI is associated with those with an estimated glomerular filtration rate of > 60 ml/min/1.73m^2. In addition, up to half of those with a baseline creatinine level of 170 mmol/liter have developed CI-AKI. The cumulative risk of several variables on renal function is still unknown despite the fact that the combination of two, or more risk factors is rather common in daily practice. This dictates the need for a global assessment of the impact of these variables on the development of CI-AKI. Appropriate risk stratification is the cornerstone of prevention of CI-AKI. Therefore, Mehran et al. [18] conducted an excellent study to develop a simple risk score that could be readily applied by clinicians to evaluate the individual patient's risk to develop CI-AKI. The scoring system, as shown in figure 1, included multiple risk factors which are hypertension, intra-aortic balloon pump (IABP), congestive heart failure class III/IV, age, anemia, diabetes, the number of contrast media, and high serum creatinine or low eGFR [18].

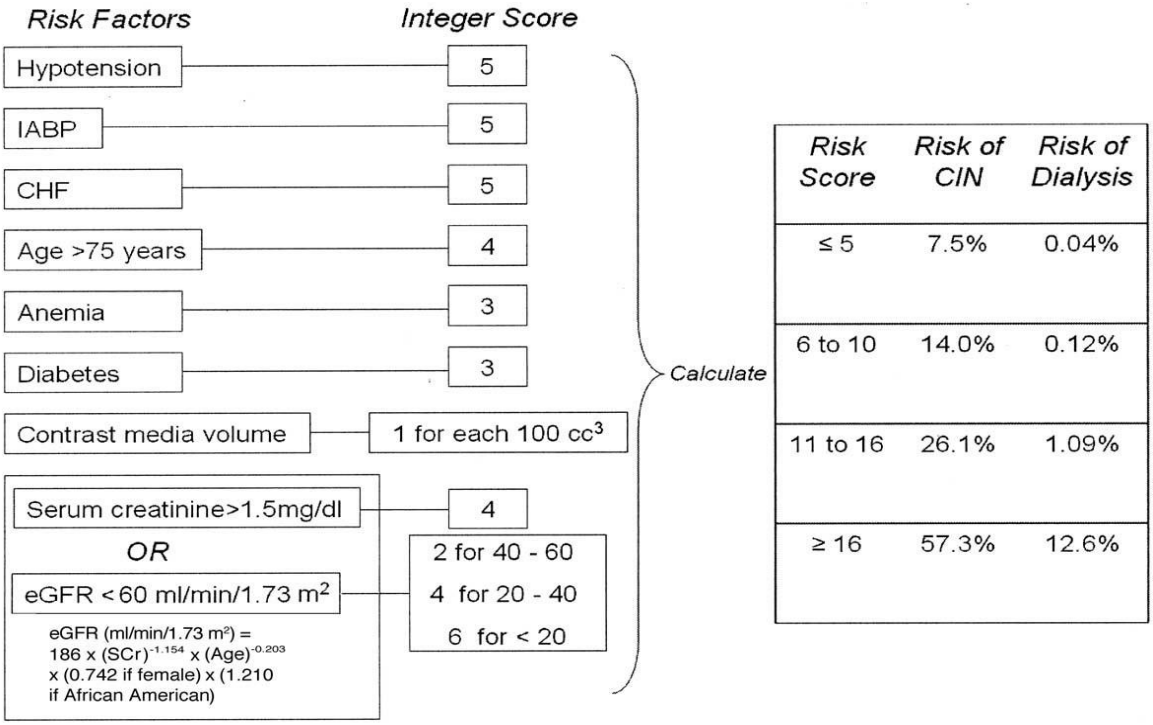

Figure 1: risk score for CI-AKI by Mehran et al. [18]

CI-AKI Prevention Measures

- **Hydration**

IV fluid hydration is the mainstay of practice in CI-AKI prevention. The most common hydration solution used is normal saline. The risk of developing adverse effects is very low and it is cost-effective as well. Studies have shown that IV hydration with normal saline is significantly effective in the prevention of CI-AKI on a consistent basis. Fluid hydration can be administered to patients of all risk categories. In treating a patient with an estimated GFR<60 mL/min/1.73m^2, fluid hydration is considered a requirement. The mechanism of how fluid prevent CI-AKI is still poorly understood, but there are some suggested theories in the literature such as IV hydration dilutes the overall intravascular contrast load, promotes diuresis, induces vasodilation, increases intravascular volume, suppresses the renin-angiotensin-aldosterone axis, and suppresses the release of the antidiuretic hormone [19].
Mueller et al. [20] Concluded in their randomized controlled trial that isotonic hydration significantly reduces the incidence of CI-AKI. Diabetic patients, women, and patients receiving huge amounts of contrast medium appear to gain the most benefits from IV hydration, especially isotonic hydration. In addition, IV hydration has also been found to be more effective than oral hydration [20].
Guidelines for prevention of CI-AKI recommended volume expansion by rigid long-term saline infusions prior and post the intervention. Saline infusions are superior to the oral fluid intakes and they are better controlled. According to guidelines, intravenous infusions should start 6–12 hours before the intervention and be maintained for 4 hours after the intervention. For hospitalized patients, this strategy is a feasible way to achieve reliable volume expansion [14].

Katzberg and Lamba [21] conducted a large analysis and found that the recommended approach for all patients receiving IV contrast material is adequate hydration before and after intervention or imaging. Imaging examination of clinical necessity should not be withheld for the fear of CI-AKI. However, alternative imaging techniques that do not require contrast material should be seriously considered for patients with severe renal impairment [21]. The first concern in those with moderate to high risk of CI-AKI is whether an alternative imaging modality can be utilized such as non-contrast computed tomography imaging or magnetic resonance imaging.
Unfortunately, gadolinium contrast for magnetic resonance imaging scanning is not recommended in patients with kidney disease since there is a risk of rare complications after the intervention, for example, nephrogenic systemic fibrosis. It is progressive fibrosis that can severely affect different body parts like the joints and the skin. Beside the availability and the cost, this limits magnetic resonance imaging use at present but it may be a potential option in the future [22].

- **Sodium Bicarbonate**

Intravenous administration of sodium bicarbonate has also gained considerable importance in the prevention of CI-AKI, but some publications have recently found mixed results and doubted the enthusiasm. The theory behind the effect of sodium bicarbonate is that it reduces the acidification of the urine and renal medullary environment. This will subsequently decrease the rate of free radical injury. Nevertheless, there is a possibility that these sodium bicarbonate effects are resulting from simple IV hydration [22]. Zhang et al. [23] conducted a meta-analysis of 20 randomized controlled trials and found that sodium bicarbonate was more efficacious compared with intravenous hydration. However, progression to dialysis and mortality were not different [23].
Several meta-analyses have been performed. They also showed a benefit to sodium bicarbonate over normal saline with respect to CI-AKI, although the major outcomes did not differ between them, for example, the need for dialysis or death [24, 25]. Many of the analyzed publications were small in size, single-center, non-blinded, and somewhat heterogeneous in their populations. There is also some concern about publication bias [22].

- **N-acetyl cysteine**

It is a derivative of the amino acid cysteine and is considered as an antioxidant. In animal models, N-acetyl cysteine resulted in a reduction in nephropathy from nephrotoxic and ischemic effects. The use of N-acetyl cysteine in humans to prevent CI-AKI is controversial. Its sulfonyl group binds with a high affinity to free radicals and this joins with a vasodilatory effect. This is thought to be the mechanism of protection against CI-AKI. Examinations have revealed that there is a significant advantage related to N-acetyl cysteine therapy over standard treatment [26].

3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors (Statins):

Statins have revealed clear benefits in the primary and secondary prevention of cardiovascular events in patients with hyperlipidemia or CKD, not requiring dialysis. Moreover, it has been demonstrated in animal models that statins can offer protection against CI-AKI, independent of their effect on cholesterol levels. This has raised interest in using statins for the prevention of CI-AKI in high-risk populations, such as patients receiving intravascular contrast medium in the context of coronary angiography (CAG) or peripheral arterial angiography [27]. Statins modulate inflammatory responses and preserve endothelial function by maintaining nitric oxide production, reducing oxidative stress, improving plaque stability, and reducing thrombus formation, as well as apoptosis [27-29].
Vanmassenhove et al. [27] conducted a review of nine different meta-analyses and systematic reviews that have been published on the potential role of statins for the prevention of CI-AKI. They concluded that the use of statins for the prevention of CI-AKI after intravascular contrast medium administration showed some promising results despite the blurred interpretation of the data. However, due to the lack of convincing evidence, it is premature to adopt the existing guidelines and implement the pre-procedural use of statins in daily clinical practice [27].

Prognosis

After the evaluation of short and long-term outcomes associated with the development of CI-AKI, studies have shown that only 1-2% of patients who develop CI-AKI, will require renal replacement therapy. Moreover, in-hospital death is similarly very uncommon following the development of CI-AKI. Nevertheless, multiple retrospective studies have demonstrated that CI-AKI is strongly associated with an increased risk for short- and

long-term mortality [30, 31]. CI-AKI commonly increases hospital duration of stays and has been associated with increased health resource utilization. Economic analyses suggest that a single episode of CI-AKI carries a one-year cost of over $11,800. Recent data links CI-AKI with persistent renal injury in 3 months following contrast exposure as well as an increase in the rate of decline of kidney function over longer-term follow-up [30, 31].

CONCLUSION

IV fluid hydration with normal saline is the mainstay of practice in the prevention of CI-AKI. Intravenous administration of sodium bicarbonate has also gained considerable importance in the prevention of CI-AKI, but it is still not approved. Although the use of N-acetyl cysteine to prevent CI-AKI is controversial, N-acetyl cysteine remains a commonly used agent even with the absence of solid scientific evidence. The application of statins for the prevention of CI-AKI after intravascular contrast medium administration revealed some promising results, but it is still premature to implement the preprocedural use of statins in daily clinical practice. There is a need for additional well-designed and sufficiently powered randomized controlled trials to clarify these issues and to assess the risk vs benefit of all other methods for the purpose of CI-AKI prevention.

REFERENCES

1. Albeladi OA. Histochemical Study of the Effect of Glycerol on the Kidney of Male Albino Rats Treated with Gum Arabic. J Biochem Tech, 2019; 10(1): 91-97.
2. Laville M, Juillard L. Contrast-induced acute kidney injury: how should at-risk patients be identified and managed?. JN journal of nephrology. 2010 Jul 1;23(4):387.
3. Rao QA, Newhouse JH. Risk of nephropathy after intravenous administration of contrast material: a critical literature analysis. Radiology. 2006 May;239(2):392-7.
4. BERLYNE N, Berlyne GM. Acute renal failure following intravenous pyelography with hypaque. Acta Medica Scandinavica. 1962 Jan 12;171(1):39-41.
5. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. The American journal of medicine. 1983 Feb 1;74(2):243-8.
6. Thomsen HS. Guidelines for contrast media from the European Society of Urogenital Radiology. American Journal of Roentgenology. 2003 Dec;181(6):1463-71.
7. Gleeson, Tadhg G., Sudi Bulugahapitiya. Contrast-Induced Nephropathy. American Journal of Roentgenology, 2004; 183(6): 1673-689. doi:10.2214/ajr.183.6.01831673.
8. Kolonko A, Kokot F, Wiecek A. Contrast-associated nephropathy--old clinical problem and new therapeutic perspectives. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association-European Renal Association. 1998 Mar 1;13(3):803-6.
9. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN. Incidence and Prognostic Importance of Acute Renal Failure after Percutaneous Coronary Intervention. ACC Current Journal Review, 2002; 11(6): 67. doi:10.1016/s1062-1458(02)00949-2.
10. Rabbani AB, Nallamothu BK. Contrast-induced nephropathy risk assessment in real world practice. American Journal of Medicine. 2011 Dec 1;124(12):1127.
11. Banda J, Duarte R, Dickens C, Dix-Peek T, Muteba M, Paget G, Mngomezulu V, Manga P, Naicker S. Risk factors and outcomes of contrast-induced nephropathy in hospitalised South Africans. South African Medical Journal. 2016;106(7):699-703.
12. Bhatt S, Rajpal N, Rathi V, Avasthi R. Contrast induced nephropathy with intravenous iodinated contrast media in routine diagnostic imaging: an initial experience in a tertiary care hospital. Radiology research and practice. 2016;2016.
13. Cantais A, Hammouda Z, Mory O, Patural H, Stephan JL, Gulyaeva L, Darmon M. Incidence of contrast-induced acute kidney injury in a pediatric setting: a cohort study. Pediatric Nephrology. 2016 Aug 1;31(8):1355-62.
14. Fähling M, Seeliger E, Patzak A, Persson PB. Understanding and preventing contrast-induced acute kidney injury. Nature Reviews Nephrology. 2017 Mar;13(3):169.
15. Thomsen HS, Morcos SK, Barrett BJ. Contrast-induced nephropathy: the wheel has turned 360 degrees. Acta Radiologica. 2008 Jul;49(6):646-57.

16. Malik A. Prevention of contrast-induced acute kidney injury. British journal of hospital medicine. 2015 Dec 2;76(12):685-9.
17. Stevens MA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido-Allen DA, Timmis GC, O'Neill WW. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the PRINCE study. Journal of the American College of Cardiology. 1999 Feb 1;33(2):403-11.
18. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. Journal of the American College of Cardiology. 2004 Oct 6;44(7):1393-9.
19. Ellis JH, Cohan RH. Prevention of contrast-induced nephropathy: an overview. Radiologic Clinics. 2009 Sep 1;47(5):801-11.
20. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media–associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Archives of internal medicine. 2002 Feb 11;162(3):329-36.
21. Katzberg R, Lamba R. CMR2009: 4.01: Contrast-induced nephropathy after intravenous administration: fact or fiction?. Contrast Media & Molecular Imaging. 2009 Nov;4(6):270-.
22. Gupta RK, Bang TJ. Prevention of contrast-induced nephropathy (CIN) in interventional radiology practice. InSeminars in interventional radiology 2010 Dec (Vol. 27, No. 04, pp. 348-359). © Thieme Medical Publishers.
23. Zhang B, Liang L, Chen W, Liang C, Zhang S. The efficacy of sodium bicarbonate in preventing contrast-induced nephropathy in patients with pre-existing renal insufficiency: a meta-analysis. BMJ open. 2015 Mar 1;5(3):e006989.
24. Hogan SE, L'Allier P, Chetcuti S, Grossman PM, Nallamothu BK, Duvernoy C, Bates E, Moscucci M, Gurm HS. Current role of sodium bicarbonate–based preprocedural hydration for the prevention of contrast-induced acute kidney injury: a meta-analysis. American heart journal. 2008 Sep 1;156(3):414-21.
25. Navaneethan SD, Singh S, Appasamy S, Wing RE, Sehgal AR. Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. American journal of kidney diseases. 2009 Apr 1;53(4):617-27.
26. Fishbane S. N-acetylcysteine in the prevention of contrast-induced nephropathy. Clinical Journal of the American Society of Nephrology. 2008 Jan 1;3(1):281-7.
27. Vanmassenhove J, Vanholder R, Lameire N. Statins for the prevention of contrast-induced acute kidney injury. Current opinion in nephrology and hypertension. 2016 Nov 1;25(6):508-17.
28. Tonelli M, Moy L, Sacks FM, Kiberd B, Curhan G. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. Annals of internal medicine. 2003 Jan 21;138(2):98-104.
29. Lev EI, Kornowski R, Vaknin-Assa H, Ben-Dor I, Brosh D, Teplitsky I, Fuchs S, Battler A, Assali A. Effect of previous treatment with statins on outcome of patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. The American journal of cardiology. 2009 Jan 15;103(2):165-9.
30. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Sonel AF, Fine MJ, Palevsky PM. Prevention, incidence, and outcomes of contrast-induced acute kidney injury. Archives of internal medicine. 2008 Jun 23;168(12):1325-32.
31. Weisbord SD, Palevsky PM. Strategies for the prevention of contrast-induced acute kidney injury. Current opinion in nephrology and hypertension. 2010 Nov 1;19(6):539-49.