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A Systematic Review of Contrast-Induced Acute Kidney Injury

Xing Li[1], Qiong Liu[2*]

[1]The First Clinical College of Chongqing Medical University, Chongqing, China
[2]Department of Emergency, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: lixing202303@126.com, *liuqiong1966@126.com

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Abstract

Background: Contrast-induced acute kidney injury (CI-AKI) is the third most common cause of AKI in hospitalized patients. Contrast agents mainly cause acute kidney injury through hypoxic damage to renal parenchyma and toxic effects on renal capillaries and tubules. Patients with CI-AKI are more likely to experience adverse events, including longer hospital stay and costs, longer ICU stay, and higher mortality rates. This article elaborates on the definition, epidemiology, risk factors, pathogenesis, and prevention strategies of CI-AKI. **Methods:** We conducted an extensive literature search using contrast agents and AKI as keywords to identify relevant studies on CI-AKI. **Conclusion:** CI-AKI is a significant clinical challenge that requires a multifaceted approach to prevention and management. Understanding the risk factors, pathophysiology, and current best practices is essential for healthcare providers to optimize patient care and improve outcomes in those undergoing contrast-enhanced imaging procedures. Hydration therapy is currently the main prevention method, but antioxidants may also become a new strategy.

Keywords

CI-AKI, ROS, Preventive Strategies, Antioxidants

1. Introduction

CI-AKI is a common complication associated with the use of iodinated contrast media in various imaging procedures, such as computed tomography (CT), angiography, and intravenous urography. It is a significant clinical concern due to its association with increased morbidity, prolonged hospital stays, and higher healthcare costs [1]. At present, using physiological saline for hydration therapy is a commonly used clinical approach, but recent studies have shown that so-

dium bicarbonate may become a new option. Some drugs (statins, antioxidants) and remote ischemic preconditioning also have a certain role in preventing the occurrence of CI-AKI.

This article elaborates on CI-AKI from five aspects: definition, epidemiology, risk factors, pathogenesis, and clinical prevention.

2. Methods

We conducted extensive searches in databases such as Pubmed, Google Scholar, and SCI, with the main keywords being "AKI", "CIN", CI-AKI, "contrast agent", etc. Two reviewers independently reviewed the eligibility of each article.

3. Definition and Epidemiology

Contrast-induced acute kidney injury was previously most commonly defined as a 25% or more increase in serum creatinine from baseline, or an absolute increase of 0.5 mg/dl or more, 48 - 72 hours after exposure to contrast agents [2]. According to Kidney Diseases: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines, contrast-induced acute kidney injury is defined as an increase in creatinine levels of ≥0.3 mg/dl (26.5 μmol/l) from baseline within 48 hours after contrast exposure, or an increase of at least 1.5 times baseline within 7 days, or urine output below 0.5 mL/kg body weight/hour, sustained for at least 6 hours after exposure. And the severity level was graded based on urine output and serum creatinine levels [3].

Acute kidney injury (AKI) causes 2 million deaths per year and is commonly found in hospitals [4]. Relevant studies have shown that hospital-acquired AKI accounts for 22% of all AKI cases globally, while CI-AKI is the third most common cause of AKI in hospitalized patients [5]. The incidence of CI-AKI varies widely between studies (2% - 15%), depending on the definition criteria and patient population, and up to 9% of patients with CI-AKI may require dialysis; In any case, the severity of CI-AKI appears to be strongly associated with the primary clinical outcome. In-hospital mortality was reported to be 7.1% in patients with less severe CI-AKI and 35.7% in patients with AKI requiring dialysis. In addition, in a retrospective analysis of 27,608 patients treated with CA, the greater the absolute or relative increase in creatinine, the greater the risk of adverse clinical outcomes [6]. In the ICU, the increasing use of CT imaging and interventional surgery means that more patients will be exposed to intravascular iodized contrast agents. At the same time, patients are critically ill and have varying degrees of organ function impairment, which increases the risk of contrast-induced AKI [7]. Patients with CI-AKI are more likely to experience adverse events, including more hospital stays and costs, longer ICU stays, and higher mortality [1].

4. Risk Factors

Chronic renal insufficiency is often considered the most important risk factor.

According to reports, the incidence of CI-AKI is 55% higher in patients with previous chronic kidney disease who receive standard percutaneous coronary intervention, possibly due to decreased adaptability but also increased cell exposure [8]. If the same amount of CM is filtered with fewer nephrons, the exposure of individual nephrons will significantly increase proportionally [9].

Aging is associated with changes in renal structure and functional decline, indicating a higher incidence of CI-AKI in elderly patients. According to a 2014 observational study, 5 out of 13 patients over 65 years old developed CI-AKI (38.46%), while patients under 65 years old did not [10]. CI-AKI is defined as an increase of 25% or more from Scr baseline, or an absolute increase of 0.5 mg/dL, until the fifth day after contrast agent infusion.

The results of numerous related studies have confirmed that contrast agent dosage is often one of the important factors in CI-AKI. The given contrast dose is directly related to the incidence of CI-AKI. For example, in the study by Garvan C Kane *et al.* [11], it was found that the volume of patients with CI-AKI (45 ± 18 ml) was higher than that of patients without CI-AKI (31 ± 18 ml, $p < 0.0005$); Compared to patients with the highest quartile of contrast agent volume, patients with the lowest quartile of contrast agent volume are 7 times less likely to develop CI-AKI. In other reports, it was also pointed out that the incidence of CI-AKI was 2.4% in patients receiving higher CM volumes, while 0.18% in patients receiving volumes lower than the maximum calculated CM dose [12]. In addition, the osmotic pressure and viscosity of contrast agents may also play a certain role in the occurrence of CI-AKI [13].

Long term use of non steroidal anti-inflammatory drugs (NSAIDS), aminoglycoside drugs, vancomycin, amphotericin B, immunosuppressive drugs (such as cyclosporine), and loop diuretics may also increase the risk of CI-AKI, and it is necessary to avoid using them for a short period of time before and after imaging as much as possible [14].

Diabetes nephropathy is a common chronic complication of diabetes, and diabetes nephropathy is an independent risk factor for chronic kidney disease (CKD) and CI-AKI. Contrast agents can rapidly alter renal hemodynamics, leading to hypoxia and ischemia. High glucose status is a promoting factor of CI-AKI, which can enhance oxidative stress and increase ROS on the one hand; On the other hand, it can lead to dysfunction of vasoactive substances, stronger renal vasoconstriction, and insufficient oxygen supply. It will also increase the load on some ion pumps and increase oxygen consumption [15].

Genetic susceptibility is also a potential risk factor. The overview of CI-AKI pathogenesis suggests that various genes act collectively, generating either a favorable or harmful environment of pro- and anti-inflammatory cytokines, which determines the intensity of tissue damage. The most relevant genes are those related to the systemic inflammatory response [16].

5. Pathophysiology

The pathophysiology of contrast-induced acute kidney injury is complex and

involves many different mechanisms [17]. Current studies have shown that contrast agent-related acute kidney injury occurs mainly through two mechanisms: hypoxia damage to renal parenchyma (especially medullary hypoxia) and toxic effects of contrast agent on renal capillaries and tubules [18] [19].

Hypoxia and subsequent ischemia-reperfusion injury lead to a large number of oxidative products dominated by ROS and form oxidative stress, resulting in abnormal activity of proteins and enzymes, structural changes and functional damage of DNA, and lipid damage [20]. The toxicity of contrast agents mainly targets renal vascular endothelial cells and renal tubular epithelial cells, leading to increased apoptosis and necrosis [21]. Specific molecular mechanisms may include damage to organelles by contrast agents through cell membranes, mitochondrial damage, efficiency of respiratory chain reduction, release of cytochrome, and induction of apoptosis through the mitochondrial pathway [22]. Another round of oxidative stress from ROS follows after mitochondrial damage. Contrast agents affect renal microcirculation, leading to hypoxia and ischemia-reperfusion injury, followed by renal tissue damage and excess ROS production. At the same time, contrast agents have toxic effects on renal tubular epithelial mitochondria and vascular endothelium, mediating mitochondrial apoptosis pathway. ROS is a central part of this [15].

6. Preventive Measure

6.1. Hydration

The use of normal saline is currently the widely recommended method for the prevention of CI-AKI, and it includes the following effects: Volume expansion: Adequate hydration of intravenous (IV) fluids (usually isotonic saline) helps to enlarge blood volume. This results in increased renal blood flow, which reduces the risk of CI-AKI by improving the delivery of oxygen and nutrients to the kidneys. Osmotic diuretic effect: Hydration also reduces the concentration of contrast media in the renal tubules, potentially reducing the risk of tubular damage and subsequent kidney damage. Urine flow rate: Proper hydration will increase the amount of urine excreted, helping to expel the contrast agent from the renal tubules more quickly, reducing the time the kidney is exposed to potentially nephrotoxic substances [23].

At the same time, because sodium bicarbonate has an alkaline effect on urine, it can reduce the production of reactive oxygen species in CM and protect the kidneys from the invasion of cytotoxic free radicals [24]. Therefore, multiple studies have discussed this, but a large meta-analysis found that sodium bicarbonate did not reduce the risk of contrast agent induced kidney disease [25].

6.2. Antioxidant

The increase of ROS production is one of the pathogenic links of CI-AKI, which indicates that the preventive use of antioxidants has a certain basis to a certain extent. Currently, the main clinically used antioxidant is N-acetylcysteine (NAC):

a substance that directly scavenges free oxygen radicals, improves blood flow through the NO-mediated pathway, thereby dilating blood vessels, and is a precursor of glutathione synthesis [26]. Although NAC remains the most widely studied antioxidant, its efficacy is still controversial [27] [28] [29] [30]. According to a meta-analysis by Xin Kang *et al.*, intravenous injection of NAC can effectively reduce the incidence of CIN in patients with existing renal insufficiency. In patients with existing renal insufficiency, intravenous NAC treatment (OR = 0.67, p = 0.008) significantly reduces the risk of CIN, but oral NAC treatment (OR = 0.85, p = 0.26). This indicates that intravenous injection of NAC is a preferred option when patients suspect pre-existing renal insufficiency [31].

The role of vitamin C (ascorbic acid) as an endogenous antioxidant, such as a scavenger of ROS, has been clearly and repeatedly demonstrated in vitro. It can also restore the vascular response of vasoconstrictors, maintain the endothelial barrier by maintaining cyclic guanylate phosphatase and occludin phosphorylation, and prevent apoptosis [32]. Vitamin E (tocopherol) is highly lipophilic and easily incorporated into cell membranes. Its efficiency as a free radical scavenger has been intensively studied in animal models of oxidative stress as well as liver and brain ischemia/reperfusion injury. In addition, vitamin E not only interrupts the oxidation of free radicals, but also can quench singlet oxygen to improve the antioxidant capacity of oil [33]. At present, a number of randomized controlled trials have been conducted to demonstrate the effectiveness of vitamin antioxidants in preventing contrast agent-related acute kidney injury. However, there is still some controversy about whether vitamin C can reduce the incidence of CI-AKI. In some studies, vitamin C has been shown to reduce the incidence of contrast-induced acute kidney injury [34] [35], while in other clinical trials, vitamin C has failed to reduce the incidence [36] [37]. Vitamin E has also been controversial in several clinical trials for the prevention of contrast-induced acute kidney injury [38] [39] [40] [41]. However, a meta-analysis of 19 studies published in 2018 indicated that vitamin C plus saline administration could effectively reduce the risk of CI-AKI, and proved that vitamin E could reduce the incidence of contrast-induced acute kidney injury, but more research was needed. The authors also verified that there was no significant difference between vitamin C and n-acetylcysteine, vitamin C plus NAC and saline, and vitamin C plus NAC and NAC in preventing CI-AKI [42].

6.3. Statins

Statins have pleiotropic effects, including enhancing endothelial NO production; Reduce the secretion of endothelin; Reducing the production of inflammatory mediators may alleviate the renal inflammatory response caused by contrast agents; It has antioxidant properties and can reduce oxidative stress [43]. Specifically, statins can directly upregulate the expression of endothelial nitric oxide synthase (eNOS) gene by inhibiting Rho kinase vanillin vanillin phosphorylation, leading to an increase in the expression of transcription factor Kruppel like

factor 2 (KLF2). In addition, statins increase eNOS expression by activating the PI3-Akt protein kinase pathway and stabilizing eNOS transcripts in an Rho dependent manner through polya-denylation, ultimately enhancing NO production; He can also directly reduce intracellular oxidative stress, and importantly, regulate validated redox sensitive transcription pathways such as NF-k β And activate protein 1 [44]. This suggests that statins may prevent the occurrence of CI-AKI. A large-scale meta-analysis suggests that short-term statin therapy significantly reduces the risk of CI-AKI and is associated with lower postoperative SCR levels and higher eGFR. Compared to low-dose statins, high-dose statins lead to a lower incidence of CI-AKI [45]. Another meta-analysis for patients undergoing coronary angiography and PCI also indicated a significant decrease in CI-AKI in the statin group compared to the control group [46].

6.4. Other Measures

In recent years, it has also been suggested that blood purification therapy can be used to prevent CI-AKI, including hemodialysis and hemofiltration therapy. However, in a meta-analysis [47], it was pointed out that hemodialysis did not reduce the occurrence of CI-AKI. At the same time, although hemofiltration can reduce the incidence of CI-AKI [48], it requires an invasive procedure and is too expensive to be suitable for the general patient.

Remote ischemic preconditioning (RIPC), defined as transient brief episodes of ischemia at a remote site before a subsequent prolonged ischemia/reperfusion injury of the target organ, is an adaptational response that protects against ischemic and reperfusion insult [49]. It mainly prevents the production of CI-AKI: NO/nitrite through two pathways, releases damage associated proteins (DAMPS), and activates temporary cell cycle arrest in renal tubular epithelial cells [50]. Although some studies have shown that RIPC does not show superiority in preventing the occurrence of CI-AKI in patients with chronic kidney disease [51], a randomized controlled trial in 2020 indicated that RIPC, as an alternative to standard treatment, can improve serum creatinine levels in patients at risk of CI-AKI after using contrast agents [52]. Meanwhile, relevant meta-analyses also indicate that RIPC can effectively reduce the risk of CI-AKI [53] [54] [55].

7. Conclusion

In conclusion, CI-AKI is a significant clinical challenge that requires a multifaceted approach to prevention and management. Understanding the risk factors, pathophysiology, and current best practices is essential for healthcare providers to optimize patient care and improve outcomes in those undergoing contrast-enhanced imaging procedures. The occurrence of CI-AKI may lead to a significant decrease in the quality of life of patients. Due to the acute decline in renal function, patients may experience a series of symptoms such as fatigue, loss of appetite, nausea, and vomiting. From a long-term health perspective, CI-AKI

may lead to a sustained decline in renal function, develop into chronic kidney disease, and even require long-term dialysis treatment, which not only increases medical costs but may also lead to a shortage of medical resources. The use of physiological saline for hydration therapy is still the best preventive strategy, and more clinical trials are still needed to use sodium bicarbonate as a hydration regimen. Treatment methods such as statins and long-term ischemic preconditioning have a certain positive effect on preventing CI-AKI. Antioxidants (such as vitamin C, vitamin E, and NAC) can also be considered as a new clinical prevention strategy. At the same time, when using contrast agents, it is necessary to use them as little as possible.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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