

Review

Contrast Medium-Induced Acute Kidney Injury

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Key Words

Contrast medium · Acute kidney injury · Risk prediction · Serum creatinine · Neutrophil gelatinase-associated lipocalin · N-acetylcysteine · Ascorbic acid · Statins · RenalGuard™ system

Abstract

Contrast medium-induced acute kidney injury (CI-AKI) is a predominant cause of hospital-acquired renal insufficiency. With an increasing number of contrast medium-enhanced radiological procedures being performed in a rapidly increasing ageing population in the Western world, it is imperative that more attention is given to understand the aetiology of CI-AKI to devise novel diagnostic methods and to formulate effective prophylactic and therapeutic regimens to reduce its incidence and its associated morbidity and mortality. This article presents high-yield information on the above-mentioned aspects of CI-AKI, primarily based on results of randomised controlled trials, meta-analyses, systematic reviews and international consensus guidelines.

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Introduction

Acute kidney injury (AKI) affects 13–18% of all patients admitted to hospital in developed countries [1]. Contrast medium (CM)-induced AKI (CI-AKI) from radiological procedures is a predominant cause. According to the National Health Service (NHS) Kidney Care, the cost of AKI to the NHS (excluding AKI in the community) has been estimated to be between GBP 434 and 620 million per year, which is more than expenditure on breast cancer or lung and skin

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cancer combined [2]. Up to 30% of AKI is preventable through simple interventions if symptoms are spotted early and prompt action is taken. With an increasing number of CM-enhanced imaging studies being performed at present, it is important that more attention is given to understand the aetiology of CI-AKI to devise novel diagnostic methods and to formulate effective prophylactic and therapeutic regimens to reduce its incidence and its associated morbidity and mortality. It has also been estimated that raising awareness about AKI in general and delivery of optimal care could save the NHS GBP 130–186 million each year [2].

Methodology

We searched MEDLINE and the Cochrane Database of Systematic Reviews with the search terms ‘contrast induced-acute kidney injury’ or ‘contrast induced nephropathy’. We focused on randomised controlled trials (RCTs), meta-analyses, systematic reviews and international consensus guidelines where possible. Newer studies were given priority over older ones.

Definition of CI-AKI

CI-AKI is commonly defined as a rise in serum creatinine (SCr) of 0.5 mg/dl or a 25% increase from the baseline value assessed at 48 h following CM administration [3].

SCr only rises out of normal range when more than 50% of the functioning kidney mass is lost. There is a significant subset of patients which incurs insult to less than 50% of the functioning nephrons with either no or marginal clinical change in SCr. These rather modest changes in SCr have a strong association with in-hospital mortality [4]. These observations have led to modification of consensus statements such as Kidney Disease Improving Global Outcomes (KDIGO) and a call to further refinement to include as minimal diagnostic criteria such as changes in SCr as low as 0.3 mg/dl, etc. to better correlate with worsening kidney function, need for renal replacement therapy (RRT) and death [5, 6].

Incidence of CI-AKI

The lack of standardisation by which CI-AKI is defined has led to the lack of optimal estimation of disease burden. The estimated general incidence of CI-AKI is approximately 7% [7]. Its incidence may increase to >50% in the presence of risk factors such as chronic kidney disease (CKD), diabetes mellitus and nephrotoxic drugs.

Pathophysiology of CI-AKI

It is believed that CM exerts direct cytotoxic effects on renal tissue (epithelial cells and endothelial cells) by inducing renal cell apoptosis in a dose- and time-dependent manner. Generation of reactive oxygen species (ROS) drives these nephrotoxic effects of CM [8]. CM alters renal vascular function by inducing hypoperfusion, particularly in the medulla, by causing constriction of vasa recta [9]. The predominant effect in the medulla is due to its high absorptive activity, which increases its oxygen requirements. The presence of CM within renal tubules also increases the viscosity of tubular fluid, impeding its flow, leading to prolonged renal retention of CM and exposure to CM cytotoxic effects.

Risk Factors for Development of CI-AKI

The risk for development of CI-AKI can be determined prior to CM administration by consideration of the pharmacokinetics of CM and the unique function of the kidney. CM is cleared entirely by the kidney, with a half-life of a few hours. It follows that the dose of CM (volume or gram of iodine) and the half-life [increased with decreased glomerular function rate (GFR)] will determine the net exposure (volume/GFR or g of I/GFR) [10, 11].

How the patient's kidney excretes this CM is the other important variable. CM will be concentrated as it traverses through the nephron due to the extraction of solute and water. The higher concentration within the nephron will favour direct tubule toxicity. CM is also concentrated in the vasa recti as they enter the medulla as a result of the osmotic movement of water out of the vessels into the hypertonic medullary interstitium. This will enhance the vasoconstriction within the vasa recti that carry oxygen to the medulla. Any factor (see below) that facilitates the concentration of CM within the nephron and/or the vasa recti may act to magnify the toxicity of the CM and promote CI-AKI.

A decrease in renal blood flow because of hypotension, volume depletion or redistribution, congestive heart failure, or drugs (such as non-steroidal anti-inflammatory drugs) will stimulate solute/water reabsorption along the nephron and water removal in the vasa recti, increasing the risk for CI-AKI. In CKD, there are less functioning nephrons. Since these nephrons are working maximally to maintain solute balance and have little vascular reserve, they are more sensitive to ischaemic injury. Vascular reserve is also compromised in conditions like diabetes mellitus and long-standing hypertension in which endothelial dysfunction limits the ability of the vasa recti to generate NO and vasodilate. Such dysfunction is also seen in the metabolic syndrome in pre-diabetes [12]. Finally, anaemia is associated with a higher risk of CI-AKI presumably because it further exacerbates the effects of CM-induced vasoconstriction of the vasa recti with resulting medullary ischaemia.

To What Extent Does Each Risk Factor Contribute to Developing CI-AKI?

The effect of risk factors is additive, i.e. the likelihood of CI-AKI rises with an increase in the number of risk factors [13], e.g. a 50% risk of CI-AKI has been reported in the presence of all 4 independent risk factors undergoing peripheral angiography [14]. A similar additive effect for development of CI-AKI requiring dialysis has been reported [15, 16].

Effect of Type of CM on CI-AKI

High-osmolality CM are associated with a higher incidence of CI-AKI [17]. They have been replaced by low-osmolality CM (LOCM) and iso-osmolality CM (IOCM) in the Western world [6]. Whether IOCM are less nephrotoxic than LOCM remains contentious [18]. This probably stems from the fact that CM properties besides osmolality, such as viscosity, may play an important role in this variability [19].

Effect of Route of CM on CI-AKI

Intravenous and intra-arterial administration of CM is associated with CI-AKI as most intra-arterial injections of CM are intravenous relative to the kidneys [20]. CM volume is a key risk factor for CI-AKI and matters the most in high-risk patients [21]. Use of automated contrast injectors can help achieve this as it reduces the CM volume used [22].

Role of Risk Prediction for Development of CI-AKI

A number of risk scoring tools have been developed from analyses of large databases of patients exposed to intra-arterial CM during coronary angiography [15, 16, 23]. None has been validated in a prospective study. More importantly, none of these have been developed or validated in patients receiving intravenous CM. The most widely used risk assessment model reflects factors discussed above (fig. 1) and predicts the incidence of CI-AKI, need for RRT and death [15]. There is however no recommendation about the use of these risk assessment tools due to above limitations.

Short- and Long-Term Effects of Transient and Persistent CM-Related Renal Dysfunction

Both transient and persistent CM-related renal dysfunction is associated with poor prognosis for short- and long-term survival and in-hospital morbidities such as major adverse cardiac events, stroke, RRT and post-procedure length of stay [24, 25]. Patients with either type of renal dysfunction have a 2- to 3-fold increased risk of mortality compared with patients with no pre-existing renal dysfunction [24, 26]. CI-AKI in patients with CKD is also associated with increased long-term major adverse cardiac events compared with those without CKD [27]. The predictors of CI-AKI are similar in patients with and without CKD [28].

Diagnostic Testing for CI-AKI

SCr is the most commonly used biomarker, an increase in which is taken to represent a decrease in GFR. SCr has a non-linear association with GFR; the performance of this marker is associated with ascertainment bias and poor sensitivity. Since renal tubules are nearly always damaged during CI-AKI, changes in SCr and GFR do not indicate tubular (i.e. structural) damage but rather late functional damage when more than 50% of the functioning kidney mass is lost. Recent research has allowed early diagnosis of structural and functional kidney damage or a combination thereof [29, 30] in the absence of classical signs that characterise CI-AKI based on SCr changes. This includes identification of biomarkers such as NGAL (neutrophil gelatinase-associated lipocalin) [31] and KIM (kidney injury molecule)-1 [32]. In the absence of rigorous validation studies measuring the association between these novel biomarkers and clinically relevant outcomes, there are currently insufficient data to support their use for staging CI-AKI [33]. It can however be speculated that this modern approach may help identify the subset of patients with subclinical CI-AKI which display changes in other structural biomarkers but no changes in SCr and GFR [34].

Management of CI-AKI

In the absence of kidney function, and when therapeutic measures that promote the intracellular shift of potassium (such as correction of acidosis with bicarbonate, glucose and insulin infusion, and β_2 -agonists) are exhausted, an excess of potassium can only be eliminated with RRT [6]. No RCT exists on dialysis for life-threatening indications; however, there is general consensus that patients with severe hyperkalaemia, severe acidosis, pulmonary oedema and uraemic complications should be dialysed emergently. Tips for management of CI-AKI once it has developed are shown in table 1.

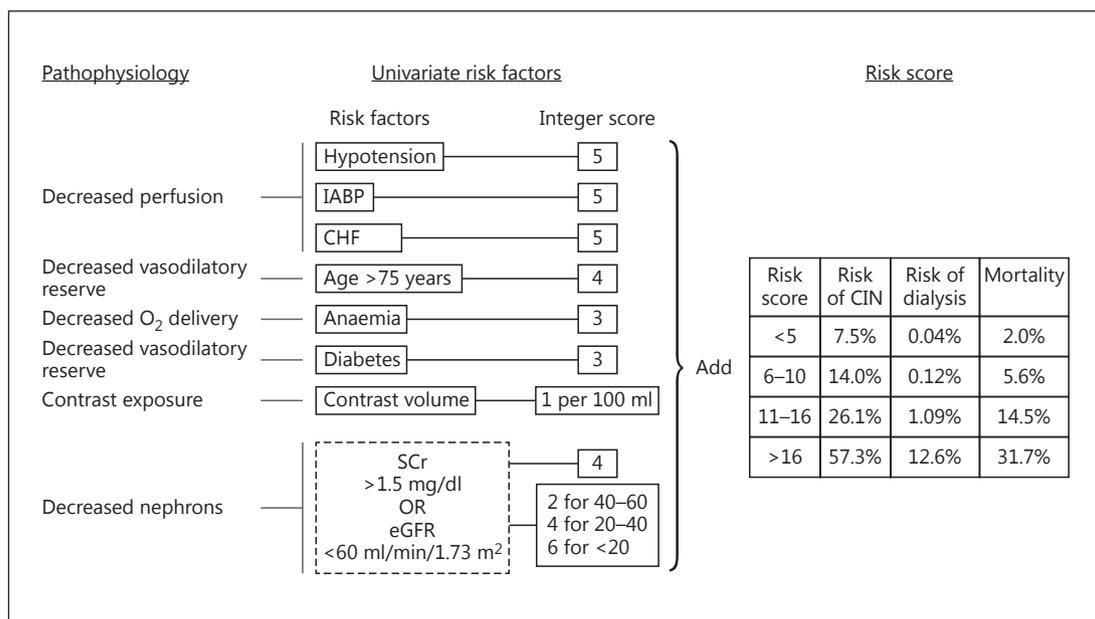


Fig. 1. The pathophysiologic basis of kidney’s vulnerability to CM exposure is reflected in the univariate risk factors for CI-AKI and creates the risk score predicting CI-AKI, need for dialysis and mortality. IABP = Intra-aortic balloon pump; CIN = contrast-induced nephropathy. Adapted from Mehran et al. [15].

Table 1. Tips for non-specialists [3]

- 1 Identify patients with recognised risk factors for developing CI-AKI.
- 2 Assess pre-procedure renal function (eGFR and SCr) before the CM examination in patients with risk factors, >70 years of age, those due to undergo intra-arterial CM administration, and known eGFR <60 ml/min/1.73 m².
- 3 Consider stopping nephrotoxic drugs such as NSAIDs and aminoglycosides.
- 4 Stop metformin based on eGFR:
eGFR ≥60 ml/min/1.73m² – continue metformin.
eGFR 30–59 ml/min/1.73m²
 Intra-arterial CM administration – stop metformin 48 h before CM administration and start 48 h later if renal function not deteriorated.
 Intravenous CM administration – continue with metformin if eGFR ≥45 ml/min/1.73m². If eGFR 30–44 ml/min/1.73 m² – as above for intra-arterial route.
eGFR <30 ml/min/1.73m² – metformin is contraindicated.
In emergency patients: stop metformin, monitor for signs of lactic acidosis and restart metformin after 48 h of CM if renal function unchanged from the pre-imaging level.
- 5 Nephrotoxic role of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is controversial, and at present there is no strong evidence to stop these before CM administration.
- 6 Intravenous volume expansion with saline, with or without additional sodium bicarbonate supplementation is the only recommended prophylaxis against CI-AKI.
- 7 Determine eGFR and SCr 48–72 h after CM examination in high-risk patients.
- 8 Discuss with nephrologist if CI-AKI is identified.

Prophylactic Measures against CI-AKI

Since our understanding of the pathophysiology of CI-AKI suggests a complex interplay of vascular and tubular effects, this makes it unlikely that a single intervention will always be successful.

Volume Replacement

To overcome the reduction in renal blood flow secondary to CM exposure, volume replacement is recommended in patients at high risk for developing CI-AKI [6] at an infusion rate of 1.0–1.5 ml/kg/h for at least 6 h before and after CM administration [3]. Normal saline (0.9%) appears to be more effective than half-normal saline (0.45%) [35]. This regimen however is impractical in the outpatient setting.

In an effort to overcome this limitation, the use of pre-procedure oral hydration followed by post-procedure intravenous hydration in patients admitted for catheterisation studies on the day of procedure has been reported [36]. Since adequately powered trials are awaited, oral hydration alone is yet not recommended [6].

Volume replacement with saline hydration seems to offer nephroprotection against CI-AKI by plasma volume expansion, reduction in renin activation, loss of nitric oxide, reduced production of ROS and through dilution of CM within the tubular lumen. The subsequent decrease in renin and vasopressin may increase urine flow rates that can reduce the CM concentration in tubular fluid.

Sodium bicarbonate-based saline hydration has been found superior to intravenous saline hydration alone [37] and is recommended [6]. This is based on the hypothesis that since CM administration increases the oxidative stress and increases generation of free radicals and ROS in the presence of acidic environment, alkalinising renal tubular fluid with bicarbonate would be a logical strategy to reduce renal injury. The most common protocol used in the literature is 3 ml/kg/h for 1 h before and 1 mg/kg/h for 6 h after procedure. This protocol is quicker than the intravenous saline hydration protocol and hence more practicable in an outpatient setting [3].

Intravenous volume expansion with saline, with or without additional sodium bicarbonate supplementation, is the only recommended prophylaxis against CI-AKI.

Diuretics

Theoretically, use of diuretics (furosemide and mannitol) as a prophylactic strategy against CI-AKI may decrease its severity by preventing renal tubule obstruction and reduction of oxygen consumption by inhibition of the Na-K-2Cl co-transporter. The administration of such agents has however been found to have either no or deleterious effects [38, 39].

The RenalGuard™ System

The cornerstone of this strategy is that hydration (to allow for intravascular volume expansion) and forced diuresis (to ensure a high urine flow rate to ≥ 150 ml/h) would result in less CI-AKI [40]. The efficacy of this technique has been reported in patients with pre-existing renal impairment only in a few RCTs [41, 42]. Large multicentre RCTs are warranted as it is unclear whether this strategy should be limited to high-risk patients or extended to all patient populations.

Antioxidants

Since ROS have been implicated in the aetiology of CI-AKI, use of antioxidants is therefore but logical. N-acetylcysteine remains the most widely investigated agent; however, its efficacy remains controversial at present [43]. Ascorbic acid has also been reported to have a nephroprotective role [44]. None of the above agents have been recommended [3].

Vasodilators

To improve blood flow to the renal medulla, vasodilators such as fenoldopam, which is a selective dopamine-1 agonist, have been used for prevention of CI-AKI, with variable efficacy [45, 46]. This has been attributed to the vasodilator-induced systemic hypotension that might have offset its localised beneficial effects on the kidneys [47]. Targeted renal therapy with direct delivery of such agents to the kidneys via renal arteries during interventional radiological procedures has been reported to overcome such potential limitations [48]. Reduction in the incidence of CI-AKI has been reported with its use [49]. However, its efficacy and safety remains untested in a planned RCT and hence is not recommended [6].

Statins

Pleiotropic effects of statins have been explored to offer nephroprotection against CI-AKI and have shown promise with a high-dose short-term use of these agents [50]. At present however there are no recommendations on their use [6].

Renal Replacement Therapy

Haemodialysis has been observed to increase the risk of CI-AKI [51]. This may result from either RRT-related toxicity caused by activation of inflammatory reactions or release of vasoactive substances on blood-membrane contact that may induce acute hypotension and renal ischaemia. Also RRT may not be able to remove CM quickly enough to prevent renal injury. At present, prophylactic RRT is not recommended [6].

Development of and adherence to institutional protocols based upon the evidence presented above have been shown to reduce the incidence of CI-AKI [52]. However, even with national protocols, adherence requires continual monitoring and effort [53].

Questions for Future Research

- Routinely used definitions of CI-AKI have limitations as they fail to define it in terms of hard clinical outcome such as the need for RRT, rather than by the occurrence of a specific decline in the renal function. An evidence-based definition of CI-AKI in terms of clinical outcome is awaited.
- Prospective validation of risk assessment tools for CI-AKI is required in well-performed large-sample-size prospective studies in patients undergoing coronary and peripheral angiography and in those exposed to intravenous CM.
- Currently, no ideal biomarker of renal impairment exists. An ideal biomarker would be diagnostic (i.e. specific) for CI-AKI, an 'early' indicator (i.e. sensitive) of CI-AKI, correlate with the degree of injury over time and be a simple, standardised and widely available assay that is cost effective with a rapid turnaround time.
- Strategies such as statins, targeted renal therapy with vasodilators and the RenalGuard™ system have shown promise but need well-performed multicentre RCTs before they can be recommended.

Conclusions

CI-AKI may occur in patients exposed to CM and has a general prevalence of approximately 7%. It is associated with clinically significant adverse outcomes including progressive loss of kidney function, need for dialysis, increased length of hospitalisation and death. The risk for developing CI-AKI can be determined prior to the index procedure by careful consid-

eration of the risk factors. Intravenous volume expansion with saline, with or without additional sodium bicarbonate supplementation, is the only recommended prophylaxis against CI-AKI.

Disclosure Statement

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