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META-ANALYSIS

Contrast-induced acute kidney injury in kidney transplant recipients: A systematic review and meta-analysis

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Abstract

AIM

To evaluate the incidence of contrast-induced acute kidney injury (CIAKI) in kidney transplant recipients.

METHODS

A literature search was performed using MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from the inception of the databases through July 2016. Studies assessing the incidence of CIAKI in kidney transplant recipients were included. We applied a random-effects model to estimate the incidence of CIAKI.

RESULTS

Six studies of 431 kidney transplant recipients were included in the analyses to assess the incidence of CIAKI in kidney transplant recipients. The estimated incidence of CIAKI and CIAKI-requiring dialysis were 9.6% (95%CI: 4.5%-16.3%) and 0.4% (95%CI: 0.0%-1.2%), respectively. A sensitivity analysis limited only to the studies that used low-osmolar or iso-osmolar contrast showed the estimated incidence of CIAKI was 8.0% (95%CI: 3.5%-14.2%). The estimated incidences of CIAKI in recipients who received contrast media with cardiac catheterization, other types of angiogram, and CT scan were 16.1% (95%CI: 6.6%-28.4%), 10.1% (95%CI: 4.2%-18.0%), and 6.1% (95%CI: 1.8%-12.4%), respectively. No graft losses were reported within 30 d post-contrast media administration. However, data on the effects of CIAKI on long-term graft function were limited.

CONCLUSION
The estimated incidence of CIAKI in kidney transplant recipients is 9.6%. The risk stratification should be considered based on allograft function, indication, and type of procedure.

Key words: Acute kidney injury; Kidney transplantation; Contrast-induced nephropathy; Contrast-induced acute kidney injury; Transplantation

Core tip: We conducted this meta-analysis to assess the incidence of contrast-induced acute kidney injury (CIAKI) in kidney transplant recipients. The estimated incidence of CIAKI is 9.6%. The estimated incidence of CIAKI in recipients who received contrast media is highest at 16% with cardiac catheterization, followed by 10% with other types of angiogram, and 6% with computed tomography scan. The findings from this study may impact the risk stratification for administration of contrast media and CIAKI prevention in kidney transplant recipients.

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INTRODUCTION

Contrast-induced acute kidney injury (CIAKI), or contrast-induced nephropathy (CIN), is associated with a significant increase in mortality and morbidity in patients with native kidneys[1-7]. The incidence of CIAKI has been reported from 2% in the general population without risk factors, to more than 20% in high-risk patients[1,8-12]. The overall frequency of CIAKI is approximately 150000 patients each year worldwide[13]. The number of diagnostic studies and procedures with iodinated contrast media including computed tomography (CT) imaging, coronary angiography, and other types of angiograms have increased for the past decade[14].

Renal transplant recipients are at an at increased risk for developing post-contrast AKI[15] since they have a lower average estimated glomerular filtration rate (GFR) and higher prevalence of diabetes and cardiovascular disease when compared to the general populations[16]. Furthermore, the majority of kidney transplant recipients are receiving calcineurin inhibitors, which are known to cause renal afferent vasoconstriction[17-20]. For these reasons, the American College of Radiology (ACR) Committee on Drugs and Contrast Media 2015 manual consider renal transplant recipients as a potentially higher risk population for CIAKI[21], and thus clinicians may be reluctant to administer iodinated contrast to renal transplant patients[22]. However, unlike the general population, the incidence and risk factors for CIAKI in kidney transplant recipients are not well studied.

The aim of this meta-analysis was to assess the incidence and risk factors of CIAKI in kidney transplant recipients.

MATERIALS AND METHODS

Cheungpasitporn W and Thongprayoon C individually examined published studies and conference abstracts indexed in MEDLINE, EMBASE, and the Cochrane Database from the inception of the databases through July 2016. The search strategy used is detailed in the supplementary material (Supplementary material 1). Further pertinent studies were retrieved by conducting a manual search using references from the articles that were identified from the search strategy noted above. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses[23] and previously published guidelines[24,25].

The inclusion criteria were as follows: (1) randomized controlled trials or observational studies; (2) patient population age $\geqslant$ 18 years old; and (3) and additional data on kidney transplant recipients were provided. The search was limited to English-language studies. Both published studies and conference abstracts were incorporated. Study eligibility was independently determined by the two investigators mentioned above. Differing decisions were settled by joint agreement.

A standardized information collection form was utilized to derive the following data: The first author of each study, year of publication, study design, country where the study was conducted, number of kidney transplant recipients studied, definition of CIAKI, number of CIAKI patients, and age and gender of CIAKI patients.

Statistical analysis

MetaXL software (EpiGear International Pty Ltd)[26] was utilized for data analysis. The incidence rates (IRs) and 95%CIs of adverse effects were reported using a DerSimonian-Laird random-effects model[27]. A random-effects model was implemented due to the high likelihood of inter-study variances. The Cochran *Q* test was completed to assess statistical heterogeneity. The I^2 statistic was added to evaluate the degree of variation across studies related to heterogeneity instead of chance. An I^2 of 0%-25% represents insignificant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity and > 75% high heterogeneity[28]. Bias funnel plots to assess for publication were used[29].

RESULTS

Our search strategy yielded 1664 articles. Of these, 1495 articles were excluded following the review of title and abstract based on relevance and the eligibility criteria. The remaining 169 articles underwent full-

Table 1 Main characteristics of the studies included in this meta-analysis[19,30-36]

Characteristics	Light *et al*[30]	Peters *et al*[31]	Ahuja *et al*[32]	Agarwal *et al*[33]
Country	United States	United States	United States	United States
Year	1975	1983	2000	2009
Total number	34 (very early post-transplant (2-24 d)	93	33	57
Male sex	NR	NR	NR	74%
Mean age (yr)	NR	NR	42 ± 2.1	58.2 ± 10.1
Baseline creatinine (mg/dL)	NR	NR	2.3 ± 0.25	1.7 ± 0.8
Immunosuppression	Azathioprine, methylprednisolone with/without anti-thymocyte globulin	Azathioprine, prednisone with/without anti-thymocyte globulin	Cyclosporine (94%)	Mycophenolate (52.6%), tacrolimus (33.3%), azathioprine (26.3%), sirolimus (1.8%), cyclosporine (52.6%)
Procedure	Drip infusion urogram from 2-24 d post-transplantation	Intravenous pyelogram (87), allograft angiogram (6) during 2 mo post-transplantation	Coronary angiogram (6), CT scan (11), peripheral vascular angiogram (11), allograft angiogram with angioplasty (5), pulmonary angiogram (1), intravenous pyelogram (1)	Cardiac catheterization
Contrast used	30% meglumine diatrizoate	NR	High osmolar contrast (The volume of contrast used was not reported)	Low-osmolar contrast (36), iso-osmolar contrast (21)
Hydration	NR	NR	78.7% of patients received IV hydration	All patients received pre-procedural intravenous hydration with bicarbonate prophylaxis used in 14 patients
CIAKI definition	An increase of SCr > 0.4 mg/dL within 4 d after contrast	Oliguria or increase in creatinine within 12 d after contrast	An increase of SCr > 25% from baseline	An increase in SCr of ⩾ 25% or 0.5 mg/dL within 3 d post-catheterization
CIAKI (%)	11 (32.4%)	45 (48.4%)	7 (21.2%) Coronary angiogram 3/6 (50%) Angiogram 2/17 (11.8%) CT 1/11 (9.1%) IVP 1/1 (100%)	9 (15.8%) 13.2% in eGFR < 60% and 21.1% in eGFR > 60%
Dialysis (%)	2 (5.9%)	NR	0 (0%)	1 (1.8%) (temporary dialysis)
Risk factor for CIAKI	CIAKI was more common and more severe in those with impaired kidney function. Kidneys from older donors were at higher risk for CIAKI	CIAKI was common in the early post-transplant period, but no increased risk was found > 120 d post-transplant	IV hydration prior to contrast exposure was protective against CIAKI; 15% of patients who received IV hydration had CIAKI *vs* 49% in non-IV hydration group	Low osmolar contrast OR 7.75 (1.10-infinity) Use of NAC OR 0.29 (95%CI: 0.04-1.78)
Outcomes	NR	NR	NR	One patient received temporary dialysis

AKI: Acute kidney injury; CIAKI: Contrast-induced acute kidney injury; GFR: Glomerular filtration rate; NAC: N-acetylcysteine; NR: Not reported; SCr: Serum creatinine.

length review, and an additional 161 were excluded for failing to meet the eligibility criteria. Eight articles[19,30-36] that met all inclusion criteria were identified for our study of CIAKI in kidney transplant recipients (Table 1). Our search methodology and selection process were outlined in Figure 1.

CIAKI definition

All included studies[19,30-36] identified CIAKI occurrence by either change in serum creatinine (SCr), GFR, or the need for dialysis after administration of contrast media, as shown in Table 1. All included studies, except by Light *et al*[30] and Peters *et al*[31], defined CIAKI as an increase in SCr of > 25% from baseline and/or ⩾ 0.5 mg/dL after 48 to 72 h. This definition is also widely used for the diagnosis of CIAKI in general patient population[37].

incidence of CIAKI in kidney transplant recipients

The incidence of AKI and severe AKI requiring dialysis after contrast exposures in kidney transplant recipients within the eight individual studies ranged from 1.8% to 48.4% and 0% to 5.9%, respectively.

Two early studies by Light *et al*[30] and Peters *et al*[31] included patients who had contrast exposure in the early post-transplant period (within 1-2 mo) and reported incidences of CIAKI of 32.4% and 48.4%, respectively. Since AKI is common in the early post-transplant period, and it is difficult to differentiate CIAKI from other causes such as calcineurin inhibitor toxicity, dehydration, acute tubular necrosis, acute allograft rejection and surgical related etiologies[32], we omitted the aforementioned two studies and performed a meta-analysis of CIAKI incidence utilizing the remaining six

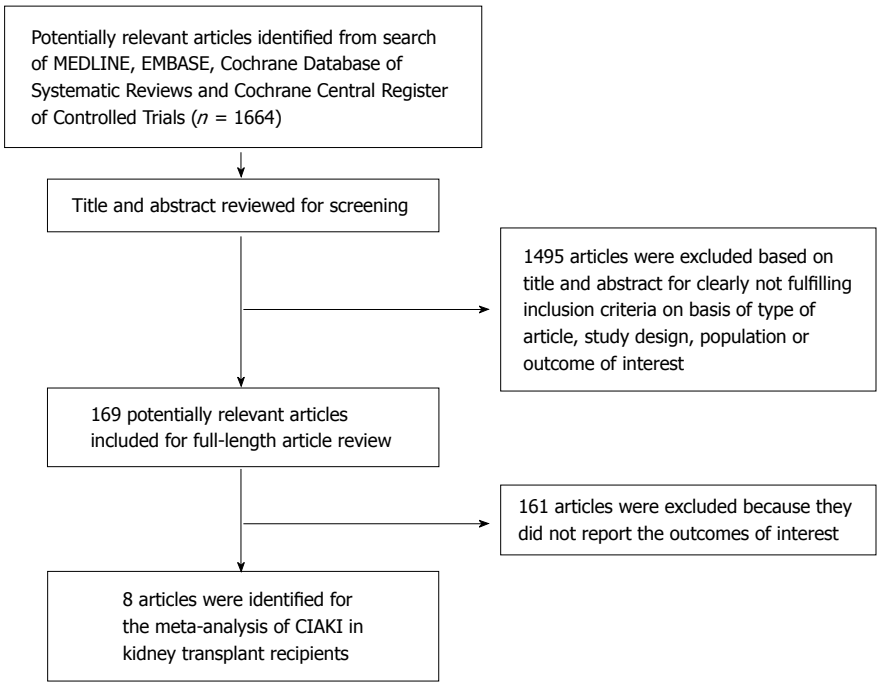

Figure 1 Search strategy. CIAKI: Contrast-induced acute kidney injury.

studies[19,32-36] with 431 kidney transplant recipients. These studies were conducted in the era of calcineurin inhibitor-based immunosuppression in kidney transplant patients with stable baseline serum creatinine before contrast administration. The estimated incidence of CIAKI was 9.6% (95%CI: 4.5%-16.3%) with evidence of a high level of heterogeneity (I^2 = 75%, P < 0.001; Figure 2). The estimated incidence of CIAKI requiring dialysis was 0.4% (95%CI: 0.0%-1.2%, I^2 = 0%). We performed a sensitivity analysis limited only to studies[19,33-36] that used low-osmolar or iso-osmolar contrast; this estimated incidence of CIAKI was 8.0% (95%CI: 3.5%-14.2%, I^2 = 72%).

Types of procedure or intervention with contrast media

The types of procedure or intervention with systemic contrast media administration in our meta-analysis of CIAKI incidence included CT scan (59.1%), coronary angiogram (23.1%), other types of angiogram (17.6%), and intravenous pyelogram (IVP) (0.2%).

Subgroup analyses by types of procedure were also performed. The estimated incidences of CIAKI in kidney transplant recipients who received contrast media with cardiac catheterization, other types of angiogram, and CT scan were 16.1% (95%CI: 6.6%-28.4%, I^2 = 40%), 10.1% (95%CI: 4.2%-18.0%, I^2 = 0%), and 6.1% (95%CI: 1.8%-12.4%, I^2 = 60%), respectively. Fananapazir *et al*[35] specifically studied the CIAKI in kidney transplant recipients who underwent allograft angiogram and reported the incidence of CIAKI of 8.1%. Data on the incidence of CIAKI in kidney transplant recipients, who underwent IVP, were limited as shown in Table 1. The incidence of CIAKI in patients who received IVP during early post-transplant period ranged from 32.4% to 100%[30-32].

Risk factors and prevention measures for CIAKI

Studies have identified early post-transplant period, older donor kidney, impaired baseline GFR, and lack of prophylactic volume hydration as potential important risk factors for CIAKI in kidney transplant recipients[30,31,38]. Ahuja *et al*[32] reported a CIAKI incidence of 15% in kidney transplant recipients with intravenous (IV) hydration before contrast exposure *vs* 49% in the non-IV hydration group. Despite limited data on the use of sodium bicarbonate and N-acetylcysteine (NAC), these studies did not find associated significant protective effects on the incidence of CIAKI[19,33,34,36].

Regarding the type of radiocontrast, high-osmolar contrast was associated with a higher incidence of CIAKI[32]. Compared to iso-osmolar contrast, Agarwal *et al*[33] found that low osmolar contrast was associated with increased CIAKI risk in kidney transplant recipients with an OR of 7.75 (1.10-infinity). In the setting of allograft angiogram, there was an increased incidence of CIAKI in recipients undergoing allograft angiogram alone (25%) compared to those who had allograft angiogram with stenting (0%).

Data on patients' comorbidities and the risk of CI AKI were limited. Abu Jawdeh *et al*[36] reported an association between low hemoglobin and increased risk of CIAKI[36]. Recently, Haider *et al*[34] found no significant effects of diabetes mellitus, age, race, gender, baseline SCr, ACE inhibitor, angiotensin receptor blocker, or diuretics use on the incidence of CIAKI. In addition, studies did not find a significant association between calcineurin inhibitor use and CIAKI[33,36].

Effects of CIAKI on renal allograft function and/or allograft failure

Although there were reported cases of severe CIAKI

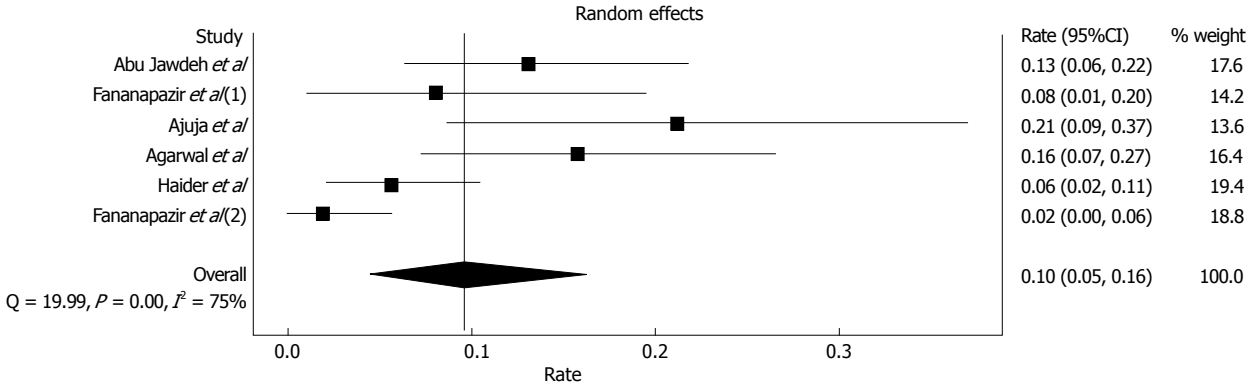

Figure 2 Forest plot of incidence of contrast-induced acute kidney injury in kidney transplant populations.

requiring dialysis[30,33], no studies reported persistent renal allograft failure requiring dialysis. Fananapazir *et al*[19,35] reported no graft loss at 30 d post contrast media administration with CT scan and renal allograft angiogram. Haider *et al*[34] reported that kidney allograft function returned to baseline in five of the seven patients who developed CIAKI within three weeks[34]. In two patients, SCr continued to be elevated due to recurrent AKI episodes from other causes. Data on the effects of CIAKI on long-term graft function or survival were limited.

Evaluation for publication bias

Funnel plots evaluating publication bias for the incidence of CIAKI in kidney transplant recipients demonstrated slight asymmetry of the graph and thus suggested the presence of publication bias for positive studies regarding the incidence of CIAKI.

DISCUSSION

In this meta-analysis, we demonstrated that overall incidence of CIAKI and CIAKI-requiring dialysis in kidney transplant recipients were 9.6% and 0.4%, respectively. The type of procedure with contrast media affected the CIAKI incidences, with estimated incidences undergoing cardiac catheterization, other types of angiogram, and CT scan of 16.1%, 10.1% and 6.1%, respectively. While no graft losses were reported within 30 d post-contrast media administration, data on the effects of CIAKI on long-term graft function were limited.

The incidence of CIAKI has been ranged from 1% in the general population without risk factors to 10%-20% among high-risk patients (especially those with diabetes and CKD)[1,2,8-12]. Not surprisingly, the incidence of CIAKI in kidney transplant recipients from our meta-analysis is relatively similar with those reported in the general adult high-risk populations since transplant recipients also have lower GFR and greater prevalence of diabetes and hypertension than the overall general population[17-20].

Our meta-analysis demonstrated higher rates of CIAKI in kidney transplant recipients who underwent cardiac catheterization and other angiograms than in those who had CT scans. These differences are likely due to intra-arterial contrast administration which may expose the kidney to higher contrast concentrations[39]. In addition, catheter manipulation may provoke atherosclerotic microemboli to the kidney[19]. Despite the higher rate of AKI and the requirement of temporary dialysis after cardiac catheterization[33], our study found no allograft failure noted at 30 d. After a CIAKI event, renal allograft function usually returns to baseline unless the patients develop recurrent AKI episodes from other causes[34]. Thus, our study supports findings from previous studies that coronary angiography is safe with respect to allograft function[40,41].

Renal allograft angiogram is performed for assessment and treatment of allograft renal artery stenosis, pseudoaneurysms, and arteriovenous fistulas[35]. Renal angiogram, which requires contrast media to be directly administered into the graft renal artery, correlates with a CIAKI risk of only 8.1% and is unassociated with any reported cases of dialysis or renal allograft failure[35]. Interestingly, allograft angiogram alone was associated with a higher incidence of CIAKI than allograft angiogram with stenting[35]. It is possible that improved renal allograft function from treating graft renal artery stenosis with stenting ameliorated the nephrotoxicity of iodinated contrast media[35].

Although renin-angiotensin-aldosterone system inhibitors/blockers and calcineurin inhibitors were studied as potential nephrotoxic medications that were commonly discontinued perioperatively, or before systemic contrast exposure due to concern for their afferent arteriolar vasoconstriction effect[42], the evidence from our study does not currently support withholding these medications prior to contrast studies. In addition, reduction of immunosuppression may put the recipients at risk of allograft rejection. Data on preventative measures for CIAKI in renal transplant recipients is limited. As in general patient populations, optimization of volume status with adequate hydration before contrast exposure may help prevent CIAKI. There was also no supported data on the use of sodium bicarbonate and NAC to prevent CIAKI in kidney

transplant recipients.

There are several limitations to our study. First, there were statistical heterogeneities in the analysis of the incidence of CIAKI. The potential sources of this heterogeneity included differences in baseline characteristics, types of procedure, and contrast media. Thus, we performed a sensitivity analysis of studies which only used low-osmolar or iso-osmolar contrast and a subgroup analysis of different procedure types, which yielded lower levels of heterogeneity. Second, selection bias may occur as contrast administration could have been avoided in patients with significantly reduced GFR. This effect may be due to the observation that most patients in the included studies had reasonable renal allograft function (eGFR > 30 mL/min per 1.73 m^2). In addition, most included studies assessed the incidence of CIAKI in a relatively low risk kidney transplant population. Although several studies have suggested safety of contrast administration in patients with significantly reduced GFR[35,43,44], more studies involving high risk patients are needed to make more definitive conclusions. Finally, data on the effect of CIAKI on long-term graft function and allograft survival are lacking. Further studies elucidating the impact of the incidence and severity of CIAKI on long-term allograft outcomes will influence clinical management.

In summary, our meta-analysis demonstrates that the estimated incidence of CIAKI in kidney transplant recipients is 9.6%. Risk stratification for the administration of contrast media in kidney transplant patients include GFR estimation or measurement, clinical indication, and type of procedure. Future studies are needed to further evaluate preventive strategies to reduce CIAKI and the effect of CIAKI on long-term graft function in kidney transplant recipients.

COMMENTS

Background

Renal transplant recipients have been considered at an increased risk for developing post-contrast acute kidney injury (AKI) because they have lower glomerular filtration rate (GFR), GFR and higher prevalence of diabetes and cardiovascular disease. In addition, the majority of kidney transplant recipients are currently on calcineurin inhibitors, which are known to cause renal afferent vasoconstriction. However, unlike the general population, the incidence and risk factors for contrast-induced acute kidney injury (CIAKI) in kidney transplant recipients are not well studied.

Research frontiers

It is necessary to assess the incidence of CIAKI and risk factors for CIAKI in kidney transplant recipients.

Innovations and breakthroughs

In this study, the authors demonstrated that an overall incidence of CIAKI and CIAKI-requiring dialysis in kidney transplant recipients was 9.6% and 0.4%, respectively. The estimated incidences of CIAKI in kidney transplant recipients undergoing cardiac catheterization, other types of angiogram, and computed tomography scan were 16.1%, 10.1% and 6.1%, respectively. No graft losses were reported within 30 d post contrast media administration.

Applications

The data in this study demonstrates an estimated incidence of CIAKI in kidney transplant recipients of 9.6%. Risk stratification for administration of contrast media in kidney transplant patients includes GFR, clinical indication, and type of procedure. While adequate hydration prior to contrast exposure may help to reduce CIAKI risk, there is currently no evidence for withholding renin-angiotensin system and calcineurin inhibitors prior to contrast studies. In addition, there is no supportive data on the use of sodium bicarbonate and N-acetylcysteine to prevent CIAKI in kidney transplant recipients.

Peer-review

Very well-written review article, the authors were investigating the incidence and risk factors for AKI in renal transplant recipients by reviewing what were published in this field.

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