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Journal of Nephrology and Transplantation

2018
Vol.2 No.1:2

Intravenous Contrast Medium-Induced Acute Kidney Injury from a Feared Complication to Non-Existence?

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Received date: March 21, 2018; **Accepted date:** April 17, 2018; **Published date:** April 21, 2018

Citation: Nyman U (2018) Intravenous Contrast Medium-Induced Acute Kidney Injury from a Feared Complication to Non-Existence? J Nephrol Transplant Vol.2: No.1: 2.

Abstract

Contrast-induced acute kidney injury (CI-AKI) has been a great concern since the 1970s and considered a leading cause of hospital-acquired AKI as late as 2002. This has now been questioned, especially following contrast medium-enhanced CT. Though the nephrotoxicity of previous high osmolar contrast media (CM) has been proven in randomized studies, several recent propensity score-matched controlled observational studies have failed to show any association between AKI and modern CM, which may be true for iso-osmolar but not for low osmolar CM. The studies have been criticized due to their retrospective nature, which makes selection bias a serious concern, and their evidence value has been graded as low. We are concerned regarding the recently revised European and American guidelines lowering the CI-AKI risk threshold to 30 mL/min/1.73 m^2 and omitting non-renal risk factors based on such studies. The lack of association between AKI and modern CM given intravenously at CT may also be a result of a better adherence to existing guidelines with proper patient selection and preventive measures We advocate prospective studies with careful analysis of the etiology of AKI in individual cases, propensity matching of patients with different CM dose/GFR ratio or controlled studies in patients who as a routine are planned for CT with and without CM.

Keywords: Kidney injury; Nephrotoxicity; Diagnostic; Radiology

Introduction

Contrast medium-induced nephropathy (CIN), recently renamed contrast medium-induced acute kidney injury (CI-AKI) [1] has become a highly controversial subject. As late as 2002 it was considered a leading cause of hospital-acquired acute kidney injury (AKI) [2]. However, recent propensity score (PS) matched controlled studies comparing patients undergoing computed tomography (CT) with and without intravenous (IV) iodine contrast media (CM) found no association between AKI and CM administration and have questioned the existence of CI-AKI [3-5]. The studies have been criticized due to their retrospective nature, which makes selection bias a serious concern [6,7]. Thus, there is still a great need for proper prospective studies to establish to what extent CI-AKI exists, since this will have a great impact on whether to use CM or not with subsequent implications on diagnostic accuracy. The aim of the present paper is to give a historical review, to discuss the studies questioning the existence of CI-AKI, to present two cases of possible CI-AKI and to propose some layouts for future prospective studies.

Literature Review

Historical review

1920s to 1950s: Organic iodine contrast media (CM) for intravascular use have been employed in diagnostic radiology since the late 1920s [8,9]. Occasional cases of uraemia after intravenous pyelography (IVP) were reported during the 1940s and early 1950s [10,11]. The rare publications of AKI following IVP was probably due to the fact that CM was seldom used in patients with impaired renal function simply because IVP yielded too low CM concentration with insufficient diagnostic information. During the 1950s AKI following aortography and renal angiography was reported [12] and was found to be the most common serious complication following abdominal aortography in a 1957 published survey [13]. From the mid-1950s new less toxic tri-iodinated salts of benzoic acid were gradually introduced e.g. diatrizoate, iothalamate, ioxithalamate and metrizoate [14], today classified as high osmolar CM (HOCM).

Increased contrast-nephropathy

1960-1970s: In the early 1960s it was demonstrated that the urinary tract could be visualized in patients with renal failure when IVP was performed using larger doses of the new tri-iodinated CM and did not seem to cause any further deterioration in renal function [15]. However, with the increasing use of large doses of CM for IVP, angiography and CT an increasing number of AKI were reported during the 1970s [16,17]. Byrd and Sherman [16] reported a mean dose of about 1.2 gram of iodine per kg among those who developed AKI corresponding to roughly 300 mL of 300 mg I/mL in an 80 kg individual. The possible pathogenetic significance of CM hyperosmolality (1500-2100 mOsm/kg H2O at 300-370 mg I/mL) was outlined and apart from large CM doses postulated risk factors were prior renal insufficiency, diabetes mellitus, advanced age and dehydration [16,17].

"Low osmolar" contrast media

1980s: Today's "low osmolar" CM (LOCM; 520 - 900 mOsm/kg H2O at 300-370 mg I/mL) was introduced during the first half of the 1980s [18]. Randomized studies including a meta-analysis [19,20] showed that LOCM caused a lower incidence for AKI than HOCM in patients with impaired renal function undergoing intra-arterial (IA) CM injections, mainly cardiac examinations. This supports a casual association with AKI for HOCM. The presence of diabetes in the now classical "Iohexol Cooperative Study" in coronary angiography [19] tripled and quadrupled the risk of AKI in patients with renal insufficiency when LOCM and HOCM, respectively, was used. Today diabetes is ignored as a risk factor for CI-AKI in recently revised international guidelines [1,6,21,22] with the motivation that it may also cause AKI in patients not subjected to CM. However, it seems unlikely that all cases of AKI in diabetics in the above cited study should have been solely caused by uncontrolled diabetic disease, but rather that the presence of diabetes potentiated the nephrotoxic effect of CM. In the meta-analysis by Barrett and Carlisle [20] LOCM was, however, less likely to prevent AKI after IV CM injections [20].

"Iso-osmolar" contrast media

1990s: During the mid-1990s the iso-osmolar CM (IOCM) iodixanol, iso-tonic to plasma (290 mOsm/kg H2O) at all concentrations, was marketed [18]. Meta-analyses of prospective randomized studies have shown a beneficial renal effect of iodixanol relative to LOCM in general [23-25] or only when compared with the LOCM ioxaglate or iohexol [26-32] following IA injections, most commonly coronary angiography/interventions. In one meta-analyses no difference in the incidence of AKI was found among various LOCM [33]. Meta-analyses of IV studies have not disclosed any significant difference between IOCM and LOCM regarding renal toxicity [24, 25]. The lack of difference in IV studies may partly be due to the fact that many high-risk patients such as those with unstable renal function, heart failure, hemodynamic instability, uncontrolled diabetes, recent CM examinations, etc. are often excluded in randomized CT studies [34-37].

Venous versus arterial injection

2000s: The next step in the discussion about CI-AKI was sparked by a critical literature analysis in the mid-late 2000s where it was concluded that "controlled series that support the hypothesis that IV administered CM is potentially nephrotoxic are conspicuously absent" [38] and one study demonstrated that serum creatinine (s-creatinine) in hospitalised patients not exposed to CM increased about as often as in published series of patients receiving IV CM [39]. This lead to editorials [40,41] and guidelines [42] claiming that the risk of CI-AKI is lower with IV than IA CM injections. This has been questioned simply because the vast majority of IA injections, i.e. selective arterial and infrarenal aortic, are IV relatively to the kidneys since the CM has to pass the local capillaries, draining veins and pulmonary circulation before reaching the systemic circulation and the kidneys [43], so called "second pass renal exposure" [21]. This also includes coronary arteriography and interventions where only a minor portion of the CM will reach the kidney directly from regurgitation into the aorta during each coronary injection or if a left ventriculogram is performed [43]. Subsequent studies comparing the incidence of AKI following IV and IA injections have not been able to demonstrate any significant differences [44-48]. In another retrospective study IV CM was associated with higher 30-day and overall mortality than IA CM administration after adjustment for comorbidities, CM dose, medications and total hydration [49]. One explanation for this difference might be that IV injection of the total CM dose for 30 seconds or less at CT results in a much higher injected dose rate than e.g. multiple small IA injections during a prolonged coronary procedure [43].

Supra- and juxta-renal aortic and selective renal injections as well as left ventriculograms are true IA CM exposures of the kidneys, so called "first pass renal exposure" [21] and should pose a greater risk of CI-AKI than injections that are IV relative to the kidneys. Higher plasma CM concentrations with higher nephrotoxic potential will strike the kidneys, especially if plasma hypertonic solutions are used with possible vascular endothelial injuries [50] and crenation of red blood cells [51] that may affect microcirculation.

Present Controversy

Does contrast-nephropathy exist?

2010s: The last step in the CI-AKI history now includes an increasing number of retrospective controlled observational studies comparing the incidence of AKI in patients undergoing CM-enhanced CT with controls subjected to unenhanced CT. A recent meta-analysis of 28 such studies [52] including those with PS-matching to control for background risk factors [3-5,53-55] found no association between AKI, need for renal replacement therapy or mortality. This has lead to the conclusion that iodine CM may not be the causative agent of

AKI following IV CM administration [3-5]. The evidence for such a conclusion has been questioned [7] and graded as low in a systematic review [6] based on the retrospective nature of the studies, which makes selection bias a serious concern. The vast majority of controls were inpatients that may have suffered from diseases with extra high risk of AKI motivating repeated s-creatinine analysis as well as steering them into non-enhanced CT or no CT at all [4,56]. There may also exist an indication bias for CM-enhanced CT if the physician feels that the patient is at low risk of AKI. The CM cohort may have been more likely to have received intravenous hydration or other preventive measures. PS-matching including comorbidities extracted based on ICD-9 codes is not perfect and cannot account for unmeasured confounders, may not be able to discriminate severity of a disease and may have been entered at any time of hospital admission, even after AKI developed. Some of the methods used to analyze data has also been criticised including the use of relative instead of absolute glomerular filtration rate (GFR) values, insufficient attention being paid to risk stratification according to CM dose or rather CM dose/GFR ratio as well as non-renal risk factors [57,58]. Finally, no attention in the meta-analysis [52] was paid to subgroup analysis which in certain studies indicated an increased risk of AKI following CM-enhanced CT in patients with impaired renal function [53,59] or in intensive care unit patients compared with controls [60]. Thus, we are concerned regarding the recently revised European and American guidelines lowering the CI-AKI risk threshold to 30 mL/min/1.73 m2 and omitting non-renal risk factors based on studies with low grade evidence and since the apparently low incidence of post-CT CI-AKI [61,62] may simply be a result of adherence to previous guidelines with proper patient selection and preventive measures.

A recent study found a similar risk of AKI among patients with ST-segment-elevation myocardial infarction who underwent percutaneous coronary intervention compared with patients receiving fibrinolysis or no reperfusion and who were not exposed to CM [63].

The authors emphasized the risk of selection bias though PS-matching was used, and the results should only be viewed as exploratory and hypothesis generating.

Analysis of Individual Cases

CI-AKI is a condition generally defined as a decrease in renal function occurring within 3 days after intravascular CM administration in the absence of an alternative aetiology [42]. In the clear majority of IV CM studies on CI-AKI, controls not receiving CM are lacking [38,64]. The lack of analyzing the cause of AKI in uncontrolled CI-AKI studies and ascribing any increase in s-creatinine beyond a certain threshold (most commonly 44 µmol/L or 25%) to the effects of CM have quite rightly been criticised [38,56]. On the other hand, it has not been analyzed on an individual patient basis in the controlled studies among those receiving CM [3-5]. Thus, statistics in large cohort studies, only focusing on the group risk, may hide a true individual risk (“terror of mean”) but in today’s era of personalized medicine one must focus on the individual risk (https: //en.wikipedia.org/wiki/Personalized_medicine). Thus, we may have to start all over again with carefully analysis of possible etiological factors of AKI in each individual case to find out whether CI-AKI still exists or not. This is illustrated by two cases (Box 1 and 2) encountered in the authors’ clinical practice.

Discussion

Both illustrated patients were outpatients in stable condition at the time of the CT examination without any signs of unstable hemodynamic, renal function or other unstable background conditions that may have caused AKI. There was no sudden change in medication. The marked increase in s-creatinine, 806% and 238% from baseline, respectively, certainly excludes the possibility of normal s-creatinine fluctuations [65]. In our opinion this makes it difficult to neglect iodine CM as a major etiological factor. Noticeably both cases had an estimated GFR (eGFR) well above the threshold value for the risk of CI-AKI in the recently revised European [6,21,22] and American [1] guidelines, i.e. 30 mL/min/1.73 m2. In addition, this threshold does not seem to take the notorious unreliability of eGFR into consideration with 20-30% of estimates having an error exceeding 30% of measured GFR [66,67].

Chronic heart failure and diabetes mellitus have consistently been identified as risk factors for the development of AKI following IV CM injections based on multivariate analysis in uncontrolled studies [6] as well as non-steroidal anti-inflammatory drugs (NSAID) in one meta-analyses [62]. However, international guidelines no longer regard them as specific for CI-AKI due to lack of rigorous testing [1,6,21,22]. Both our illustrated cases had such risk factors, but with no acute deterioration of these conditions that may have caused the AKI. In our opinion there is still no evidence against the possibility that e.g. diabetes and chronic heart failure may potentiate a nephrotoxic effect of CM as already discussed [19] and are therefore still included among as risk factors for CI-AKI in the 2017 revised guidelines of the Swedish Society of Uroradiology CM committee [68].

It has been argued that the exaggerated fear of CI-AKI and withholding CM with resultant lessening of diagnostic information may be considerable [56]. On the other hand, CM are according to our experience many times used indiscriminately at CT for convenience with the argument "not risk missing anything" and without considering e.g. the very low prevalence of disease for a certain indication. Case 2 is a typical example of such unnecessary use of contrast media when the only issue was to measure the diameter of the aorta in a screening situation.

Though the European Society Urogenital Radiology guidelines states that "there is insufficient evidence that dose is a problem with intravenous CM" [21], the CM dose should nevertheless be as low as reasonable achievable for a diagnostic study considering that CI-AKI is a toxic effect. In case 1 mapping of the central venous system may have been possible to obtain by direct CT venography following injection

of diluted CM, e.g. 50 mL of 30 mg I/mL through a peripherally inserted venous cannula in the symptomatic arm. Such a concentration corresponds to about 750 HU at 120 kVp (25 HU per mg I/mL) [69] and would have resulted in a total dose of 3 instead of 45 grams of iodine. Another option to reduce the CM dose at CT is to apply low kilovoltage technique [70-72].

LOCM nephrotoxic but not IOCM?

Both patients in the present report received LOCM. It should be noted that in one PS-matched controlled study IV LOCM was found to be a nephrotoxic risk factor in patients with eGFR <30 mL/min/1.73 m2 with a trend toward significance at 30-44 mL/min/1.73 m2. Bruce et al. [59] found that the LOCM iohexol caused a higher risk of AKI after CM-enhanced CT than the IOCM iodixanol at s-creatinine levels >1.8 mg/dL (160 µmol/L) while there was no difference between iodixanol and the control group above that level. Also Tong et al. found similar incidences of AKI when using iodixanol for CT and IA cardiac catheterizations compared with patients undergoing non-enhanced CT as controls [48]. Interestingly McDonald et al. [3] used iodixanol at creatinine levels above 2.0 mg/dL (175 µmol/L) when concluded that CM may not be the causative factor of AKI. In a later controlled study [73] they found no differences in the incidence of AKI, dialysis, or mortality between PS-matched patients with the highest perceived risk of AKI undergoing iodixanol enhanced CT and non-contrast CT. They also reported that patients in their prior studies [3,4,55,74], with predominantly LOCM, had fewer illnesses, fewer CKD and ICU patients, and were therefore at lower risk of developing CIN than patients in the iodixanol cohort. This may then explain why no difference in the rate of AKI after LOCM compared with controls was found in the studies by McDonald et al.

In an ischemic kidney model in pig's renal artery injections of CM with the highest osmolality and lowest viscosity caused hemorrhagic congestions, necrosis and markedly decreased renal function while the iso-osmolar CM with the highest viscosity (iodixanol) affected renal function no different than saline [75-77]. These results and the fact that porcine kidneys are more like human kidneys than kidneys of most other species [78] also contradicts the view that the high viscosity of IOCM should be a significant pathophysiological factor in CI-AKI [79].

Thus, instead of concluding that CI-AKI following CT may not occur one may as well conclude from these studies that it may occur when using LOCM but may not occur when using iodixanol and adequate prophylaxis. Reasons for the lack of difference in the incidence of AKI between iodixanol and LOCM in meta-analyses of randomized CT studies have already been discussed.

Future Studies

How should we then move forward to obtain better evidence regarding whether CI-AKI exists or not? As indicated by the present case examples one option would be to prospectively perform post examination creatinine measurements in patients with certain defined risk factors and then carefully analyze individual cases of AKI to find out if CM is the only reasonably cause of AKI.

Instead of using patients undergoing non-enhanced CT as controls with the inherited risk of selection bias, a second option has been proposed based on the ratio between the gram-iodine CM dose and GFR [57], a crucial measure regarding toxicity of drugs excreted by glomerular filtration like CM [80,81]. The analysis may then be restricted to the CM-enhanced CT group and to propensity match patients with different dose/GFR ratios at various GFR stages [57]. Such PS-matching most likely reduces the problem of selection bias, since all included patients have received CM but at different CM dose/GFR ratios.

A prospective controlled trial is a third option, though randomization of patients to receive either CM or saline would in general be unethical for obvious reasons; CM may be crucial for adequate diagnosis, control patients will be subjected to two examinations with a week interval, one without and one with contrast medium with doubling the radiation exposure, and double blinding would be impossible [82]. However, considering the magnitude of importance of the CI-AKI issue in diagnostic radiology there might be at least one group of patients where a prospective controlled trial might be ethically acceptable, e.g. elderly (60 years) patients with malignant diseases undergoing regular surveillance with CM-enhanced CT. In many instances both non-enhanced and CM-enhanced CT is performed in this patient group. By performing the two phases with a week interval the patient would also be its own control. This group may also be of special interest since they may be on nephrotoxic chemotherapeutics and the rate of AKI has been correlated significantly with IV CM [83] and appear higher in patients with recent chemotherapy [84].

Conclusion

Recent PS-matched retrospective controlled observational studies questioning the existence of CM nephrotoxicity following CM-enhanced CT suffer from several methodological concerns. Lowering the GFR threshold of CM-nephrotoxicity to 30 mL/min/1.73 m2 in international guidelines seems premature considering the low level of evidence of such studies and the unreliability of estimated GFR. Our two patient reports indicate that CM is an etiological factor to AKI following CM-enhanced CT. Optional approaches to study the possible existence of CI-AKI may include careful prospective analysis of the aetiology of PC-AKI in individual cases, restricting PS-matching to patients receiving CM with various CM dose/GFR ratios at different GFR levels or performing a prospective controlled study in patients with malignant disease scheduled for routine tumour surveillance without and with CM-enhanced CT, but with a week interval.

Box 1

Case 1: A 60-year old overweight woman with diabetes mellitus, hypertension and macroproteinuria (u-albumin/u-creatinine ratio 62 g/mol) was admitted to the emergency

department because of a swollen arm. She was on antidiabetic medication, loop diuretic, amlodipine and ibuprofen (800 mg x 2) but none was initiated recently. There was no treatment with renin-angiotensin system (RAS) inhibitors. Her general condition was stable with no breathing difficulties, chest pain, nausea, vomiting or hemodynamically instability. A deep venous thrombosis was suspected. S-creatinine at admission was 109 µmol/L with an estimated GFR (eGFR) of 45 mL/min (45 mL/min/1.73 m2). Ultrasonography was inconclusive why phlebography was performed with a LOCM and a total dose of 90 mL 300 mg I/mL. No thrombosis was diagnosed. The patient left the hospital in stable condition and was informed to discontinue her metformin and ibuprofen medication. S-creatinine prior to re-starting metformin two days later had now increased to 439 µmol/L. She had also developed nausea and vomiting, noticed decreased urine output and was subsequently hospitalized. S-creatinine peaked at 987 µmol/L at day seven after which renal function started to improve with no need for haemodialysis. She was discharged after fully two weeks with a s-creatinine of 139 µmol/L. Two months later it was 121 µmol/L. The hospital cost was estimated to about 7000 Euro.

Box 2

Case 2: A 65-year old man underwent ultrasonography as part of a screening program for abdominal aortic aneurysms. The examination was inconclusive (BMI 39 kg/cm2). Instead CT of the aorta was requested. Based on a s-creatinine of 122 µmol/L three days prior to CT, GFR was estimated to 63 mL/min (48 mL/min/1.73 m2). A CM-enhanced CT was performed using 93 mL 350 mg I/mL of a LOCM. Later the same evening the patient experienced dark coloured urine with decreasing amounts. During the following days he became increasingly tired and contacted the renal ward day five. S-creatinine was now 412 µmol/L and he was admitted. He had had no signs of acute heart failure or hemodynamic instability. There were no signs of any pulmonary oedema at the CT examination and no chest x-ray was performed before or during hospitalization query cardiac failure/pulmonary oedema. He was discharged a week later with a s-creatinine of 128 µmol/L and it remained stable at one month, 140 µmol/L. The patient had type 2 diabetes mellitus with multiple complications, chronic kidney disease, restrictive cardiomyopathy and chronic heart failure with fluid restriction, none of which was mentioned on the CT request or checked by the radiology department. He was on treatment with insulin, loop-diuretic, clindamycin, paracetamol and codeine, none of which had been recently started. He had no treatment with RAS-inhibitors. No hospital cost was calculated.

Competing Interests

U.N. and P.A has received speaker's fees from GE Healthcare AB, Danderyd, Sweden.

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