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CLINICAL STUDY

Contrast-induced nephropathy after a second contrast exposure

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ABSTRACT

Background: The risk of contrast-induced nephropathy (CIN) after repeated contrast exposure has not been evaluated. *Methods*: We prospectively evaluated the effects of two contrast exposures during an investigational study of a new computerized tomography (CT) scanner. Adult subjects who underwent a variety of contrast-enhanced imaging procedures with conventional apparatus, as part of routine care, were invited to undergo a second contrast-enhanced research scan. Subjects were required to have an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 and a serum creatinine (sCr) value measured immediately prior to the second contrast exposure that was <125% of that measured prior to the first imaging study. *Results*: Twenty-eight subjects underwent a second contrast exposure after a mean interval of 20 ± 13 days (75% males, 89% Caucasians, 21% diabetics, mean age 60.6 ± 6 years, mean contrast volume 130 ± 42 mL). There was a significant increase in mean sCr and decline in eGFR after the second contrast exposure (sCr 0.93 ± 0.14 vs. 0.86 ± 0.15 mg/dL prior, $p = 0.027$; eGFR 83.9 ± 13.5 vs. 89.8 ± 13 mL/min/1.73 m^2 prior, $p = 0.028$). Four subjects (14.3% of the population) developed CIN. *Conclusion*: Even in subjects with relatively preserved renal function there is a notable risk of CIN after repeated contrast exposure. This conclusion was unaltered by several sensitivity analyses.

Keywords: contrast media; nephrotoxicity; acute kidney injury; acute renal failure

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INTRODUCTION

Contrast-induced nephropathy (CIN) continues to be a leading cause of hospital-acquired acute kidney injury.[1] In subjects with normal renal function, the occurrence of clinically detectable contrast-mediated renal injury is rare.[2] Subjects with prior renal insufficiency are at higher risk of contrast-mediated acute kidney injury. A meta-analysis of studies in patients with renal impairment exposed to low osmolar contrast agents depicted an overall incidence of CIN of 16.8%.[3] CIN is not necessarily always benign. Besides consequences of renal failure, which are only apparent in severe cases, CIN is associated with long-term clinical adverse events.[4]

However, most data regarding CIN relate to risks and event rates after a single exposure to an iodinated contrast agent. In clinical practice, it is not infrequent that patients are repeatedly exposed to contrast agents, either for diagnostic or therapeutic purposes. While intuitively it might appear that there is likely a greater risk of CIN after a second contrast exposure, the occurrence of acute kidney injury after repeated contrast exposures has never been prospectively investigated.

We studied the change in renal function and incidence of CIN in subjects undergoing two contrast-enhanced imaging procedures.

METHODS

This study is a pre-planned analysis of the renal effects of two contrast exposures during an investigational study of the image quality and potential clinical applicability of a new high-definition computerized tomography (CT) scanner.

Adult subjects (aged 18 years or more) who underwent any of the following contrast procedures as part of their routine clinical care were invited to participate: coronary arteriography, carotid/cerebral arteriography, thoracoabdominal aortic arteriography, abdominal visceral arteriography, multi-pass hepatic and pancreatic CT studies with cholangiopancreatography, CT urography, or CT enterography.

The following constituted exclusion criteria: pregnant women; age greater than 75 years; age less than 40 years for men and 50 years for women; allergy to

contrast; or enrollment in another concurrent investigational radiology study. For coronary CT angiography component, subjects who required either nitroglycerin and/or beta-blocker for the scan (used for coronary artery vasodilatation or blockade of heart rate, respectively, to enable optimal CT examination of the coronaries) but had asthma with daily use of nebulizer, systolic blood pressure less than 100 mmHg, or severe aortic stenosis were not eligible. In addition, for safety purposes, subjects could not have an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 body surface. Further, serum creatinine (sCr) was measured immediately prior to the second contrast exposure and it was mandated that this value should not be ≥25% or ≥88.4 μmol/L compared to a value obtained prior to the clinically indicated imaging study. When the study was designed and conducted, GFR estimations for purposes of inclusion were derived using the four-variable modification in diet in renal disease (MDRD) equation using sCr, age, gender, and race (African-American vs. other races).[5] The newer CKD-EPI formula was not available during that period.[6] However, after publication of the new CKD-EPI formula, which is more accurate than the MDRD formula particularly at higher GFR values, GFR data were derived using the new formula, and presented and analyzed as such. At the time of inclusion, all subjects had an eGFR > 60 mL/min/1.73 m^2, calculated by either formula.

Subjects who satisfied study criteria underwent a repeat contrast-enhanced CT study with the new prototype 64-channel high-definition CT scanner 750 HD (General Electric Healthcare Inc., Waukesha, WI, USA). The protocol mandated that the interval between the two contrast exposures should not be less than 3 days. The actual interval varied due to subject convenience and/or logistic issues. All iodinated contrast media used in the study, both the clinically indicated and investigational imaging procedure, were approved agents already available for general use. The protocol pre-specified that the contrast type and volume for the second contrast exposure would be same as that used for the first clinically undertaken imaging procedure. In the latter instance, the contrast type and volume for various types of CT scans were administered according to a pre-set protocol and were not study related. An instance in which the clinically indicated study was a direct coronary angiography, the contrast agent was used as determined necessary by the performer and was also not study related. In five instances, the contrast volume administered for the research scan was greater than that used for the clinically indicated study by an average of 18 ± 40 mL. No prophylactic intervention was employed for the prevention of CIN. Subjects were scheduled to undergo a repeat measurement of sCr and estimation of GFR 3 days after the second contrast exposure.

sCr measurements were performed by the clinical laboratory affiliated with Froedtert Memorial Lutheran Hospital (Dynacare Laboratories, Milwaukee, WI, USA). Creatinine measurements were performed using a Beckman Coulter (formerly Olympus) AU5431™ chemistry autoanalyzer (Beckman Coulter Inc., Fullerton, CA, USA) using a kinetic modification of the Jaffe procedure. Briefly, in this colorimetric reaction creatinine reacts with picric acid at alkaline pH to form a yellow-orange complex that is detected by the analyzer. The sCr method was calibrated to be traceable to isotope dilution mass spectrometry. For the first seven researches contrast exposures, the sCr measurements were reported to one decimal point, as was the routine sCr reporting procedure for the laboratory at that time, by rounding off the machine printout result to the first decimal place. Subsequently, sCr results were reported to two decimal places. These laboratory reporting changes were unrelated to the study. The laboratory personnel who ran the creatinine assays were unaware of any specifics related to a particular subject sample. Precision testing of the sCr measurements depicted a coefficient of variation of 2.3% and a standard deviation of 0.02 mg/dL for samples with a mean sCr value representative of the study population (0.89 mg/dL).

The study was approved by the Institutional Review Board (IRB) of the Medical College of Wisconsin and all patients provided informed written consent.

End points and analysis

Our pre-specified end points for the detection of contrast-mediated acute kidney injury after second contrast exposure were the change in sCr, change in eGFR, and incidence of CIN defined as a rise in sCr by at least 25%. The continuous variables (sCr and eGFR) were compared using repeated measure ANOVA followed by pair-wise comparison using the Dunnett–Hsu adjustment for more than one comparison (PROC MIXED procedure; SAS 9.2; SAS Institute Inc., Cary, NC, USA). Results are depicted as mean ± standard deviation (SD) and a p-value of ≤ 0.05 was considered significant.

Funding source and role of sponsor

The study was funded by General Electric Healthcare (Waukesha, Wisconsin, USA). The sponsor had no role in the analysis presented in this report or writing of the manuscript. The corresponding author had full

access to all the data and takes public responsibility for the data presented herein.

RESULTS

Twenty-eight subjects underwent a second contrast exposure for a research-related CT examination. During this procedure all subjects were outpatients, received contrast intravenously, and no subject was hospitalized between the research contrast exposure and post-contrast protocol sCr measurement. Thus, factors that could affect renal function during hospitalization or any question of procedure-induced atheroembolic disease were not present. The average interval between the research scan and prior contrast exposure was 20 ± 13 days. The average age of the study population was 60.6 ± 6 years, 75% were males, 89% were Caucasians, and 21% were diabetics. In all instances, a low osmolar non-ionic contrast agent was used and the mean contrast volume was 130 ± 42 mL. In four instances, the post-contrast sCr was obtained later than day 3, day 4 (n = 2), day 5 (n = 1), and day 7 (n = 1). The patient characteristics are depicted in Table 1.

There was no significant difference in either mean sCr or eGFR between the values obtained prior to the clinically indicated contrast exposure (first value) and the subsequent measurements (second value) obtained just preceding the research study (sCr 0.89 ± 0.14 vs. 0.86 ± 0.15 mg/dL, p = 0.25; eGFR 87.2 ± 14.3 vs. 89.8 ± 13 mL/min/1.73 m^2, p = 0.24, respectively; average interval between the two 28 ± 19 days). As indicated above, the second sCr value could not be greater than the first value by ≥25%, which is considered the definition of CIN, for the subject to satisfy study criteria and receive the second (research-related) contrast medium. There was a significant increase in mean sCr after the second contrast exposure (0.93 ± 0.14 vs. 0.86 ± 0.15 mg/dL prior, p = 0.027). There was also a significant decline in mean eGFR (83.9 ± 13.5 vs. 89.8 ± 13 mL/min/1.73 m^2 prior, p = 0.028). There was no difference in the conclusions related to change in GFR if the latter was calculated using the MDRD formula.

Four subjects (14.3% of the subject population) developed CIN defined as a rise in sCr by at least 25% above the pre-contrast value. In these cases the average percent rise in sCr was 42% and the average absolute rise in sCr was 0.29 mg/dL. Three contrast exposures were related to abdominal CT scans and one was related to CT angiogram of the neck (in all these instances contrast was given intravenously for both the clinically indicated and research study). Table 2 depicts measures of renal function before and after the second contrast exposure. If subjects with an interval between the two contrast exposures greater than 30 days were excluded, as arguably the effect of prior contrast exposure may have dissipated by this time, the incidence of CIN after the second exposure was 19%. There was no change in these incidence results if the difference between the post- and pre-contrast sCr was reduced by 2 SDs of the result of laboratory precision testing (i.e., increasing the pre-contrast sCr by 1 SD and reducing the post-contrast sCr by 1 SD).

We tried to discern potential differences in the incidence rates due to differences in laboratory reporting of sCr, that is, to one or two decimal places as laboratories tend to vary in this regard. In the present analysis, if all sCr values were rounded to the first decimal place, the incidence of CIN would be 17.9%. In an alternate approach, an additional decimal point was imputed in instances where sCr was reported to one decimal point in a conservative manner. For the pre-contrast value, a digit '4' was imputed at the second decimal place, and for the post-contrast value the digit '5' was imputed at the second decimal place and the reported first decimal place was reduced by '1'. For example, a pre-contrast value of 1.1 was considered 1.14 (as 1.14 would have been rounded and reported as 1.1) and a post-contrast value of 1.2 was considered 1.15 (as 1.15 would have been rounded and reported as 1.2). This sensitivity analysis essentially reduces the difference between the pre-contrast and post-contrast sCr values by 0.1 mg/dL. In such case, the incidence of CIN was slightly lower but still notably high at 10.7%.

The overall incidence of CIN was still 14.3% if one related the sCr value after the research scan with the sCr value that was measured before the first clinically indicated imaging study (first value) considering the latter as the baseline.

DISCUSSION

The study results depict that even in patients with relatively preserved renal function there is a significant risk of CIN after repeated contrast exposure within a short period of time. We detected a 14.3% incidence of CIN in such a population (average pre-contrast eGFR 89.8 ± 13 mL/min/1.73 m^2, average pre-contrast sCr 0.86 ± 0.15 mg/dL) exposed to contrast twice within an average period of 20 days. There was also a small but significant increase in the average sCr and decline in mean GFR after the second contrast exposure.

The study subjects were required to have good renal function for enrollment. Further, the imaging procedure involved necessitated relatively low dose contrast exposure than might occur in procedures

TABLE 1. Patient characteristics.

Subject #	Age (years)	Gender	Race	DM	Contrast agent	Contrast volume (mL)	Pre-contrast serum creatinine (mg/dL)	Pre-contrast eGFR
1	72	M	Caucasian	No	Iopamidol[a]	169	1	75
2	73	M	Caucasian	No	Iopamidol	130	1	74
3	51	M	Caucasian[b]	No	Iopamidol	120	0.8	103
4[c]	63	M	Caucasian	Yes	Iohexol	165	1	80
5	60	M	Caucasian	Yes	Iopamidol	110	0.8	97[d]
6	56	M	Caucasian	No	Iohexol	165	1	84
7[c]	63	M	Caucasian	No	Iohexol	165	0.7	100[e]
8	65	M	Caucasian	No	Iohexol	165	0.84	92
9	59	M	Caucasian	No	Iohexol	165	0.97	85
10	60	M	AA	Yes	Iohexol	165	0.96	99
11	61	M	Caucasian	Yes	Iopamidol	164	1.17	67
12	56	M	AA	No	Iohexol	165	0.68	123[e]
13	49	M	Caucasian	No	Iohexol[f]	75	0.73	109
14[c]	54	F	Caucasian	No	Iohexol	165	0.53	108
15	61	F	Caucasian	No	Iohexol	165	0.89	70
16	63	M	Caucasian	No	Iohexol	93	1	80
17	56	M	Caucasian	No	Iohexol	165	0.84	98
18	65	M	Caucasian	No	Iohexol[f]	65	0.96	83[g]
19	65	M	Caucasian	Yes	Iopamidol	130	0.81	93
20[c]	57	F	Caucasian	Yes	Iohexol[f]	65	0.62	100
21	65	F	Caucasian	No	Iohexol[f]	65	0.83	74
22	54	F	Caucasian	No	Iohexol[f]	65	0.7	99
23	51	M	Caucasian	No	Iopamidol	156	0.94	93
24	65	M	Caucasian	No	Iohexol[f]	75	0.97	82
25	66	M	Caucasian	No	Iopamidol	120	0.87	90
26	67	F	Caucasian	No	Iopamidol	68	0.69	90
27	63	F	Caucasian	No	Iohexol	165	0.77	82
28	58	M	AA	No	Iohexol	165	1.1	85

Notes: eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2; M, male; F, female; AA, African-American.
[a]In all instances Isovue®370 (Bracco Diagnostics Inc., Princeton, NJ, USA).
[b]Hispanic ethnicity (all others non-Hispanic).
[c]Subjects who developed contrast-induced nephropathy.
[d]Post-contrast serum creatinine obtained on day 5.
[e]Post-contrast serum creatinine obtained on day 4.
[f]Omnipaque™ 350 in these cases, all others Omnipaque™ 300 (GE Healthcare Inc., Princeton, NJ, USA).
[g]Post-contrast serum creatinine obtained on day 7.

TABLE 2. Serum creatinine and eGFR values before and after second contrast exposure in subjects who developed contrast-induced nephropathy after the research study.

Subject #	Pre-contrast serum creatinine (mg/dL)	Pre-contrast eGFR[a]	Post-contrast serum creatinine (mg/dL)	Post-contrast eGFR
4	1	80	1.3	58
7	0.7	100	1.1	71
14	0.53	108	0.73	94
20	0.62	100	0.88	73

Note: [a]eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2.

such as interventional cardiac angiography. Thus, the results might indicate that in higher risk settings, such as in subjects with underlying renal insufficiency or those undergoing higher volume contrast administration, the risk of CIN associated with repeated contrast exposure merits greater consideration. Overall, the present findings suggest that the potentially increased risk of CIN related to re-exposure to iodinated contrast media within a period of few days warrants appropriate deliberation during routine clinical care. Such deliberation should consist of assessment of risk–benefit in each particular case along with communication with the patient.

In most instances, CIN results in an asymptomatic rise in sCr that returns to baseline within a few days.[7] However, in severe cases there are consequences that include extension of hospital stay, increases in medical expenditure, and though not frequent, the need for renal replacement therapy in severe instances.[8] More recently, the potential long-term implications of CIN have aroused much interest and concern due to epidemiologic evidence that has shown poorer outcomes of subjects who develop post-contrast acute kidney injury that appear to extend beyond renal failure and its consequences. Many studies have shown poorer risk-adjusted survival in patients who develop acute kidney injury following contrast administration.[9–14] The data to date are largely observational and have not been confirmed by pre-planned randomized controlled trials. However, whether the clinical consequences and long-term risks associated with severe CIN that occurs after a second contrast exposure are different merits further study, an issue that is more relevant to subjects with pre-existing renal impairment.

The mechanisms involved in higher risk of CIN with repeated contrast exposure are not known. However, the findings raise the question that even though biochemically renal function returns to baseline, subclinical renal injury might persist and lead to a greater risk of injury with another exposure.

There are limitations of our study. The study was uncontrolled and had a modest sample size. One must be careful in attributing changes in sCr to contrast administration as such variations have also been observed in subjects not administered contrast.[15] However, these data relate to retrospective series of hospitalized subjects who are prone to variations in sCr and renal function due to a variety of reasons. The current data were prospectively obtained and all subjects were outpatients. The high incidence of post-contrast change in renal function is persistently portrayed after several sensitivity analyses. A further limitation relates to the fact that study population consisted of subjects at inherently low risk of CIN, as noted before, and thus does not provide data about the risks of repeated contrast exposure in higher risk settings or in instances in which the first exposure leads to CIN. However, it demonstrates that even in such instances a significant percent of subjects develop an acute change in renal function.

In conclusion, although the risk of CIN in subjects with a lack of significant renal impairment is low, it is not insignificant if such subjects are exposed to repeated contrast administration. In such a population we depicted a 14.3% incidence of CIN defined as rise in sCr by at least 25% after a second contrast exposure. These data raise concern that the clinical implications of contrast-mediated acute kidney injury after repeated contrast exposure could be more severe but warrant investigation.

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