The myth and reality of contrast-induced nephropathy

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Iodinated contrast media were first used in clinical radiology nearly a century ago. Shortly thereafter, their ability to permit excretory urography was recognized and this study soon became the mainstay of uroradiologic practice. For decades, little thought was given to the idea that contrast media had the potential to be nephrotoxic; indeed, for imaging patients with renal failure, increasing the contrast dose above standard amounts was advocated and practiced. But in the 1960s, reports of renal dysfunction shortly after contrast administration began to appear. Studies supporting the nephrotoxicity of contrast were published with ever-increasing frequency. By the turn of the millennium, they numbered in the thousands, and contrast became accepted as one of the most frequent causes of acute renal failure.

The rising influence of this concept was followed by the explosive rise in utilization of contrast-enhanced CT examinations. As a result, innumerable contrast-requiring radiologic exams were withheld from patients, likely at the cost of decreased diagnostic accuracy and, undoubtedly, poorer patient management. Less dramatic consequences created by concern for contrast-induced nephropathy (CIN) were the adoption of "preventive" measures, such as formal patient questionnaires and measurements of precontrast serum creatinine level or estimated glomerular filtration rate. Many cases of nephropathy were attributed to contrast, with the result that the real causes, both isolated or contributory, were not recognized or treated.

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However, in the past few years, a profound change in our understanding of this issue has occurred. The performance and analysis of clinical series using appropriate control groups have led to a reevaluation of the risk of CIN. It has become clear that the risk is much lower than had previously been thought. We are now in the midst of a change in practice. Restrictions on contrast administration are being relaxed. The consequent freedom to administer much-needed IV contrast to a wider group of patients is undoubtedly improving management and, it is hoped, leading to better patient outcomes.

Initial research

The original investigation of contrast-induced acute kidney injury began in the 1960s. For a couple of decades, most series studied patients undergoing excretory urography using high-osmolarity contrast media (HOCM). In the 1980s, 2 developments occurred. There was a gradual, but now complete, switch to low-osmolarity contrast media (LOCM) and an increasing fraction of studies began to appear from angiocardiography laboratories. LOCM is probably less nephrotoxic than HOCM,[1,2] and, if similar agents are used, intravenous-contrast examinations probably pose less of a risk to renal function than angiocardiography.[3,4] However, in estimating the risk to patients given LOCM intravenously, data from laboratories performing angiocardiography and from older studies using HOCM continue to be applied.

Countless publications have addressed factors which have been thought to increase the risk of CIN. Among these are pre-existing renal dysfunction, advanced age, hypertension, heart failure, gout, multiple myeloma, renal transplantation, dehydration, diabetes, nephrotoxic drugs, contrast dose, and administration of multiple doses of contrast during a short period. Most of these inciting factors have not been confirmed, but the sheer number of publications, along with the tendency for many readers to be aware of the earlier studies suggesting compound risk, but not of nonconfirmatory studies, have amplified concern about CIN in many practitioners' minds. Fear of CIN has been heightened by perceptions of its consequences. Post-contrast acute kidney injury (AKI) has been shown to be associated with, and widely considered responsible for, extended hospitalization, higher incidences of acute cardiovascular and neurological events, the need for long-term renal replacement therapy and even increased mortality.[5,6]

Probably the most important reason that the risk of CIN has been exaggerated has to do with improper methodology used in nearly all series published to

date. Most have been performed by determining each patient's creatinine level prior to administering contrast, selecting a threshold value for a postcontrast rise in creatinine which, if exceeded, was said to represent CIN and determining the percent of patients whose postcontrast creatinine rises exceeded that threshold. Unfortunately, this process does not distinguish between any creatinine elevations caused by contrast and those that would have occurred without contrast administration. Serum creatinine, of course, is a measure of glomerular filtration (albeit an imperfect one) and glomerular filtration rate (GFR) varies in normal individuals. In hospitalized patients (nearly all published studies have been performed on hospitalized patients), the reasons for variations in GFR are myriad. Among patients whose baseline creatinine is high, day-to-day variations in creatinine are much more pronounced than in patients whose renal function is normal.[7] If all creatinine variations after contrast are ascribed to the intravenous contrast, it will seem that contrast causes renal dysfunction much more often in patients with initially elevated creatinine, which is of course exactly what is typically observed.

Rectifying methodological error and controlling for confounders

Comparing rates of postangiocardiography AKI to post contrast-enhanced CT (CECT) AKI is difficult since there are few studies directly comparing them.[8,9] Although an extensive literature review suggests that rates of AKI are less after CECT,[10] extreme variation of results make it difficult to determine a precise risk ratio. It may be that patients who undergo angiocardiography are at higher risk of renal dysfunction resulting from hypotension, arrhythmias, myocardial infarction, atheroemboli,[11-13] and use of nephrotoxic medications, all of which are less likely to occur in patients undergoing CECT. Also, most angiocardiography patients undergo left ventriculography, during which the peak concentration of contrast in renal arterial blood is much higher, and changes much more rapidly, than when contrast is administered intravenously. In any case, we believe that rates of contrast-induced acute kidney injury (CI-AKI) reported in angiocardiographic series should not be applied to patients undergoing CECT.

The error of omitting proper control series has been a problem with virtually all reported series until 1985. Shortly thereafter, there were 2 publications,[14,15] which included control groups. These studies found no evidence that subjects receiving contrast experienced AKI any more often than control patients not receiving contrast. These experiments were not widely recognized, and their results were not incorporated into common knowledge or practice. More recently, these studies were reviewed,[16] and the legitimacy and validity of studies performed without a control group was called into question.

Since then, more observational studies have taken into account the need to have a comparison group and most of these studies have found no significant association between contrast media and renal dysfunction. In fact, some of these publications showed that patients who did not receive intravenous (IV) contrast were at higher risk of renal dysfunction after CT.[17] The latter observation led, in turn, to the recognition of the possibility that the results of controlled studies may be affected by selection bias. Most of the controlled studies used patients undergoing CT without contrast as control subjects; the clinicians who chose between contrast-enhanced and noncontrast CT examinations may have elected to avoid contrast administration in patients with borderline renal function or in those at risk of renal dysfunction like shock, diabetes mellitus, and congestive heart failure. In this scenario, patients in the noncontrast groups have worse baseline renal function and/or higher prevalence of comorbidity, including heart disease and diabetes. Thus, they are at higher risk of developing AKI even without contrast administration. It is possible that impaired renal function from causes other than IV contrast administration in these control patients masked any real tendency of contrast to cause nephropathy.

Propensity score matching of observational controlled studies to limit selection bias

To control for this selection bias, 2 independent research groups have recently compiled large cohorts in retrospective controlled studies and analyzed the data utilizing propensity-score adjustment[18], which controls for baseline differences between contrast and noncontrast groups that may affect the decision to administer contrast. One group found that postcontrast AKI only exists among patients with poor baseline renal function with serum creatinine > 1.5 mg/dL and who demonstrate a direct linear association between baseline serum creatinine (> 1.5 mg/dL) and risk of CI-AKI.[19] The other research group compiled an even larger group of patients and followed a similar propensity-score adjustment approach. They showed no significant differences in the rate of serum creatinine increase between exposed and unexposed groups.[20] Furthermore, the latter group supported their finding with a counterfactual analysis, in which each patient acted as his or her own control by having both CECT and noncontrast CT within the study period. This comparison showed no significant association between IV contrast and AKI. The authors of the second paper also conducted a systematic literature review and meta-analysis of all previously published observational controlled studies on CI-AKI and overall found no significant association of intravenous nonionic contrast material administration and later increase in serum creatinine.[21]

Both of these powerful studies are impressive and compelling. They clearly show that AKI after CECT either does not occur in hospitalized patients or at least is not as common as has been thought. Our view is that the truth probably lies somewhere in between the conclusions of these studies. However,

an exact and reliable estimate of the risk will be achievable only by a randomized controlled trial.

Unanswered question

Still, referring physicians and radiologists cannot wait for randomized clinical trials. The question as to whether a given patient should receive contrast arises daily in any busy practice. These decisions require not only an estimate of the likelihood of CIN but also a clear idea of the severity of the risk to the patient's overall health that nephropathy poses. Overall, the most common course of postcontrast nephropathy is a transient asymptomatic creatinine rise.[22] This is important: It accounts for the paucity of accounts of CIN detected among outpatients, and it probably results from the most commonly-used criterion for diagnosing CIN—a creatinine rise of 0.5 mg/dL or more within a several-day period. One certainly wouldn't expect every patient exhibiting such a rise to progress to chronic renal failure and a need for dialysis.

This is not to say that acute creatinine increases are free of associated risk. As outlined earlier, groups of patients whose serum creatinines rise have higher morbidity and mortality[5] than patients whose creatinine is stable after IV contrast administration. These observations continue to lead to reluctance to administer contrast to patients with renal dysfunction, but these associations deserve scrutiny. First of all, the experiments suggesting such grave consequences to CI-AKI have all involved patients who had undergone angiocardiographic procedures and who are sick enough to need continued hospitalization; these are patients with a number of serious medical problems. Next, most hospitalized patients have serum creatinine elevations that are not related to contrast injection.[16] Finally, the nephropathy may not cause these admittedly serious conditions, but may simply be an indicator of other coexistent serious diseases. Patients with generalized vascular disease that leads to cerebral and myocardial ischemia and death are likely to have renal dysfunction secondary to the underlying disease and not administration of contrast material.

Conclusion

Recent studies provide convincing evidence that nephrotoxicity after CECT is an unusual phenomenon in hospitalized patients. It is probably still more rare in outpatients who are generally healthier than hospitalized patients. Post-CECT nephrotoxicity occurs less frequently than after angiocardiographic procedures, and comorbid conditions may be the driving force behind post-CECT renal dysfunction. The authors do not deny the potential nephrotoxicity of IV contrast, but believe that contrast-related nephrotoxicity is infrequently an important clinical event, does not occur among healthy patients and is usually limited to transient asymptomatic elevation of serum creatinine. We also believe that it occurs less frequently than thought in patients with pre-existing renal disease (ie, serum creatinine ranging between 1.5 and 2.0 mg/dL). It is more likely to occur among patients with severe pre-existing renal disease (ie, serum creatinine > 2 mg/dL), but is still responsible for only a small fraction of instances of postcontrast AKI. Thus, we encourage more liberal use of intravenous IV contrast in radiological imaging to improve diagnostic accuracy and ultimately improve patient care.

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