Intravenous Contrast-Induced Nephropathy—The Rise and Fall of a Threatening Idea

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Contrast-induced nephropathy (CIN) has been considered to be a cause of renal failure for over 50 years, but careful review of past and recent studies reveals the risks of CIN to be overestimated. Older studies frequently cited the use of high-osmolality contrast media, which have since been replaced by low-osmolality contrast media, which have lower risks for nephropathy. In addition, literature regarding CIN typically describes the incidence following cardiac angiography, whereas the risk of CIN from intravenous injection is much lower. Most of the early published literature also lacked appropriate control groups to compare to those that received iodinated contrast, and thus attributed rises in creatinine to intravenous contrast without considering normal creatinine fluctuations (frequent in patients with kidney disease) and other acute pathologic states such as hypotension or nephrotoxic drug administration. The aim of this paper is to review the literature detailing CIN risk, discuss why CIN risk is often overestimated and how withholding contrast can lead to misdiagnosis and delay in appropriate patient management.

Key Words: Contrast-Induced Nephropathy, Acute Kidney Injury

INTRODUCTION

That iodinated radiocontrast materials carry a considerable risk of nephrotoxicity has become axiomatic for more than half a century.[1,2] Although contrast-induced nephrotoxicity (CIN) is said usually to be brief and reversible, it is also commonly believed to lead occasionally to chronic kidney failure, dialysis, prolonged hospital inpatient stays, and even to death.[3,4] As a consequence of this long-held belief, imaging examinations requiring the use of intravenous (IV) contrast are often foregone entirely.[5] Recent rigorous investigations have shown that the nephrotoxic risk of IV contrast is, in fact, much lower than has been commonly thought and, indeed, may barely exist at all.[6-9] Nevertheless, a continued fear of contrast-induced nephropathy continues to lead to withholding of contrast; this not only reduces diagnostic and therapeutic effectiveness in a variety of clinical situations but prevents episodes of acute kidney injury (AKI) from being attributed to their real causes, which in turn reduces effective management even further. The purpose of this review was to outline the level of risk erroneously attributed to contrast media, recount the reasons for the inaccurate prevailing estimates of risk, quantify the low levels of risk that obtain in reality, and call attention to the importance of changing practice to reflect actual risk levels.

Major reasons for overestimation of risk include the continued reference to risks associated with now-abandoned contrast agents, the failure to acknowledge the different incidences of nephropathy following the administration of contrast during cardiac catheterization procedures and those in which contrast is administered intravenously, and the failure to use appropriate control populations in clinical series.

HISTORY

Acute kidney dysfunction was first attributed to iodinated contrast in 1954, when Bartels and others described acute kidney failure in a patient immediately after IV pyelography. This was followed shortly by multiple publications describing kidney failure after performing the same procedure.[10-12] A growing number of reports linking contrast to AKI ensued; larger series included those from Swartz and others and Hou and others.[13,14] Some reported very high incidences: one publication found CIN in 55% of patients with pre-contrast kidney failure and in 100% of a small subset of patients with nephrotic syndrome.[15] Risk factors that were claimed to increase the risk of AKI after contrast began to appear; the list eventually included most conditions known to cause AKI on their own and to increase the likelihood of AKI when they accompanied primary causes of kidney dysfunction, including pre-existing kidney dysfunction, diabetes mellitus, hypotension, nephrotoxic drugs, diuretics, and procedures, such as intra-aortic balloon pump use.[16-18] As attention continued to be paid to the phenomenon, CIN gained a reputation as being one of the most common causes of AKI, at least in hospitalized patients.[14] Along with the kidney dysfunction, CIN came to be associated with increased rates of other kinds of morbidity, including chronic kidney failure, need for dialysis, and increased risk of death mentioned earlier.[3,4,19,20]

As CIN became more frequently investigated, the criteria adopted to define it were narrowed to a small number of frequently used ones, including absolute rises in serum creatinine (often 0.5 mg/dL; occasionally 1.0 mg/dL) and fractional rises in creatinine (commonly 50-100%) over baseline. Changes in estimated glomerular filtration rate (eGFR) were less commonly used. Criteria varied greatly with regard to the duration of a creatinine rise required to diagnose nephropathy and how long an interval between contrast administration and observation of the elevated creatinine was permitted. Despite these variations in experimental protocols, consensus formed that nephropathy most commonly consisted of a brief episode of creatinine elevation that returned to baseline levels and usually required no management.[21] With the proliferation of published series, the

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factors mentioned earlier that increased the risk of post-contrast creatinine elevation were repeatedly confirmed; among these, elevated pre-contrast creatinine levels became recognized as the most predictive of CIN.

NEPHROTOXICITY RISKS OF HIGH-OSMOLALITY CONTRAST MEDIA AND LOW-OSMOLALITY CONTRAST MEDIA

A great deal of the early work assessing the magnitude of CIN risk was done in an era when all intravascular contrast agents were hyperosmolar.[22] About 3 decades after the initial recognition of CIN, high-osmolality contrast media, which are approximately 4 times the osmolality of blood, were replaced by low-osmolality contrast media, which are about twice the osmolality of blood, and which clearly reduced the incidence of generalized contrast reactions. Studies addressing the relative risks of CIN of the 2 types are not unanimous, but there are at least some data which suggest that low-osmolality agents cause nephropathy less frequently.[23] A randomized trial evaluating the risk of nephrotoxicity in a large cohort demonstrated a 3.3 times greater risk of developing nephropathy in patients who received high-osmolar agents than those receiving low-osmolar agents.[24] Other series found only marginal improvement.[25,26] But despite this salutary observation, the risks of CIN presented in texts, reviews, and even in the discussion sections of clinical publications evaluating CIN risk commonly cite data from the era of HOCM to quantify the general risk. This tendency persists even to the most modern editions of internal medicine, nephrology, and urology texts[27-30] and is undoubtedly responsible in part for the current overestimates of the danger of CIN (Table 1).

CLINICAL SUMMARY

- Contrast-induced nephropathy risk has been overestimated in clinical practice.
- Inappropriate reference to risks of now-abandoned contrast agents, conflating risks of angiocardiography and intravenous contrast administration, and failure to utilize proper control groups have all contributed to the overestimated risk estimates.
- By avoiding the use of intravenous contrast, the risk of patient misdiagnosis is increased which can lead to worse patient outcomes.

NEPHROTOXICITY RISKS OF INTRAVENOUS CONTRAST AND ANGIOCARDIOGRAPHY

During the initial era of investigation of CIN, most publications reported series of patients who received contrast intravenously, usually for IV pyelography. Others dealt with patients who underwent diagnostic angiography, for which contrast could be administered via catheter intravenously, into the aorta, or into almost any large or medium-sized systemic artery.[31,32] After the turn of the century, however, series investigating kidney function after contrast administration in the course of cardiac catheterization procedures began to appear more frequently, and the majority of publications switched from those being written in radiology departments to those produced by interventional cardiology practices.[33,34] Thereafter, investigations dealing with the incidence of CIN, risk factors affecting its incidence and prophylactic measures to reduce the likelihood, and severity of CIN have largely dealt with transcatheter cardiac and coronary procedures.

Comparing the levels of CIN risks encountered after IV contrast administration and after cardiac catheterization procedures has been difficult. Indications are different for the 2 classes of procedures so that similar patient cohorts cannot be assembled, preparation procedures including premedication protocols differ, contrast doses are different, injection protocols (sites, number of injections, injection rates and number of injections per procedure), and exact prophylactic measures usually do not match. In addition, the technical aspects of interventional cardiac procedures can pose multiple risks to kidney function, which are usually absent during IV contrast administration; these include hypotension and/or altered cardiac output, arrhythmias, renal arterial embolization caused by aortic atheromas dislodged during catheter advancement and withdrawal, and peripheral hemorrhage.[35]

Given these differences, it seems intuitive that cardiac catheterization procedures pose a higher risk to kidney function than does IV contrast administration.[36] Attempts to compare them are relatively few, but there is evidence that nephropathy does, in fact, occur more frequently after cardiac catheterization[24] than after IV contrast administration.[25,37,38] Nevertheless, texts, reviews, and individual paper discussion sections often treat the risk of nephropathy caused by contrast as if differences in procedures attending the contrast administration did not matter and as if the risks of contrast administration were the same for all procedures.

ESTIMATION OF CONTRAST RISK WITHOUT AND WITH CONTROL GROUPS

The most important reason that the risk of contrast nephropathy has been exaggerated is the nearly ubiquitous lack of control groups in the clinical series published during the first 4 decades of the investigation of CIN. Nearly all these studies were designed in a similar fashion: after measurement of serum creatinine, a cohort of patients would receive contrast, and additional creatinine determinations would be performed in the days after contrast administration. A threshold of creatinine rise would be chosen and the fraction of patients whose creatinine serum values rose to or beyond that threshold would be assessed, and the "risk" of contrast nephropathy would be declared equal to that fraction. This reasoning is a classic example of the *post hoc ergo propter hoc* (after this, therefore because of this) fallacy; the possibility that an increase in creatinine might have occurred for reasons other than contrast administration was rarely acknowledged.[39]

As mentioned earlier, pre-existing kidney failure has come to be recognized as the best predictor of increased likelihood of post-contrast creatinine rises. It had been long recognized that day-to-day creatinine variations are larger in patients with kidney failure than in those with