Preventing Complications of Radiographic Contrast Media: Is There a Role for Dialysis?

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ABSTRACT

Nephrologists are often called upon to provide hemodialysis to remove radiographic contrast media in patients with chronic kidney disease (CKD) – usually but not exclusively, those with end-stage renal disease. The reasons for this request vary from concerns over the volume load associated with the administration of a hyperosmolar solution, to the renal and extra-renal toxicities of the contrast itself. Simple calculations demonstrate that the increase in extracellular volume after a typical contrast load is minimal. Data supporting the extra-renal toxicity of contrast in patients maintained on dialysis are lacking. Iodinated contrast agents have molecular weights of 700–1500. This relatively small size as well as their lack of protein binding makes them well suited for removal with extracorporeal renal replacement therapies. Thus, provision of hemodialysis immediately following a contrast load is often utilized in an attempt to prevent further renal damage in patients with advanced stages of CKD. A number of trials have failed to demonstrate that this maneuver is effective. Hemofiltration (HF) has been reported to decrease the risk of acute renal failure in patients with CKD receiving a contrast load, but the studies are methodologically flawed. Therefore, there is currently no sound basis for routinely recommending hemodialysis (or HF) in patients at high risk for contrast media-associated complications.

I would wager that every nephrologist has gotten the phone call at least once: Dr. Get-in-the-way wants to be assured that your patient will be dialyzed after a radiographic procedure, or he or she will not do the study. I am certain that the radiologist has nothing but the best intentions. But are these concerns well founded? If not, these encounters that continue to plague those in practice can be frustrating and even annoying. In this review, I will attempt to identify the issues and explore the data concerning the use of renal replacement therapies in the removal of iodine-containing contrast media in patients with chronic kidney disease (CKD).

There are three concerns in regard to the administration of contrast to individuals with impaired renal function. The first relates to the volume load associated with the intravascular administration of the contrast itself. The other two concerns are related to the direct toxicity of contrast to (a) remaining functional nephrons, and to (b) nonrenal tissues.

Contrast preparations are of variable molecular structures that determine markedly different osmolalities when put into solution (Fig. 1). The original contrast preparations (e.g., sodium diatrizoate) are ionic molecules, with osmolalities of 1400–1800 mOsm/l in solution, and are now termed "high-osmolar." Second-generation substances are nonionic, reducing the osmolalities of these agents to 500–850 mOsm/l, and are referred to as "low-osmolar" contrast agents (e.g., iohexol, iopamidol, and iodipamide). The newest class of contrast agents is made up of dimers, combining two nonionic contrast molecules into one molecule through a common side chain, thus reducing the number of particles by one-half and allowing a further lowering of the osmolality of the contrast solution ("iso-osmolar, e.g., iodixanol, 270 mOsm/l) (1).

Symptoms directly associated with intravascular contrast administration include nausea, vomiting, flushing, and hypotension. These symptoms appear to be related to the osmolality of the agent used as they are seen less commonly in patients receiving the lower osmolality agents. Anaphylaxis is an unusual but more serious complication, often associated with a history of an "allergy" to iodine or shellfish. It also appears to occur less commonly with the nonionic contrast agents (2).

Doses of radiographic contrast administered vary by radiographic procedure.; a typical dose for an abdominal computed tomography scan is 125 ml. A coronary angiogram with stent placement may use in excess of 200 ml of contrast. Contrast preparations are not lipophylic. After injection into the vascular tree there is rapid mixing in the intravascular compartment. This is followed by diffusion into the extracellular extravascular (interstitial) space. Contrast media are not metabolized and excretion is through the kidney alone. As radiocontrast does not enter cells, the administration of a high- or low-osmolar contrast media (both being hyperosmolar) creates an osmotic disequilibrium between the extracellular and intracellular compartments, and water must move out of the cells to achieve osmotic equilibration (3). Thus, the acute effect on extracellular volume will be greater than the actual amount of contrast that was injected. Individuals with normal renal function may respond with an osmotic diuresis. Diuresis in those with renal impairment may be limited with the resultant increase in intravascular volume risking a state of fluid overload.

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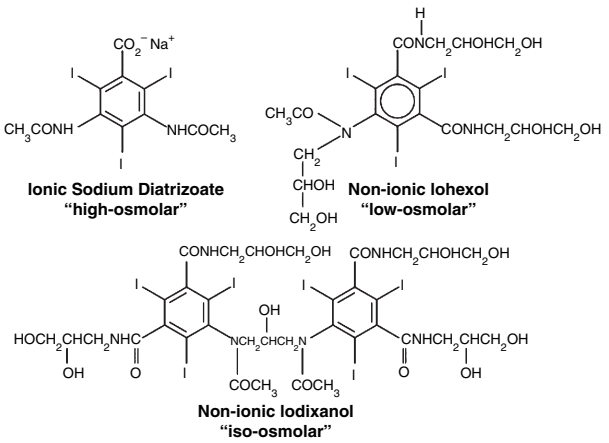

Fig. 1. Molecular structures of commonly used contrast media. The high-osmolar contrast media are monomers that are ionized, thus increasing osmolality in solution. The low-osmolar molecules are nonionic and significantly reduce the osmolality. The iso-osmolar contrast preparations combine two nonionic contrast molecules providing more iodine moieties/molecule and thus requiring fewer molecules. This translates into fewer particles in solution reducing the osmolality to a level similar to plasma.

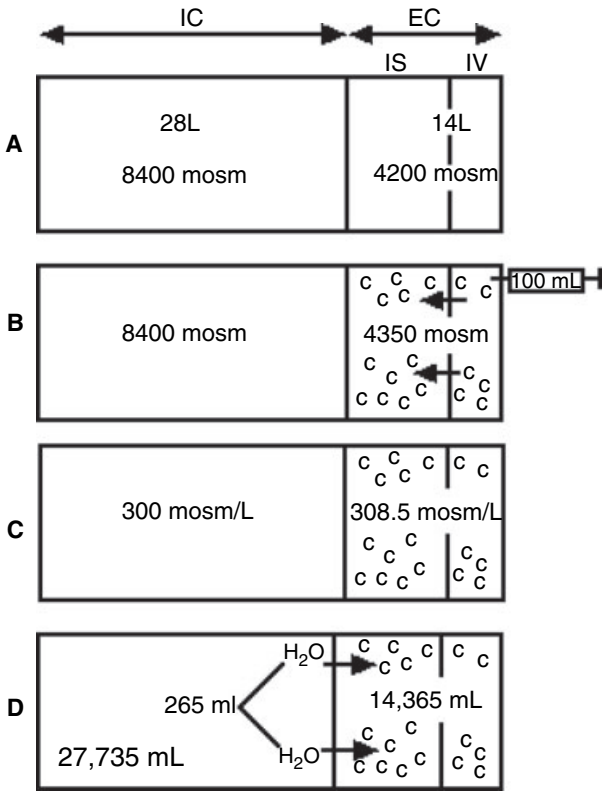

Fig. 2. The effect of hyperosmolar contrast media on the size of fluid compartments within the body. (A) Precontrast fluid compartments in a 70-kg person, 60% water, two thirds intracellular (IC) and one third extracellular (EC), plasma osmolality 300 mOsm/l. Of the EC compartment, two thirds is interstitial (IS) and one third intravascular (IV). (B) 100 ml of 1500 mOsm/l contrast (c) is injected into the IV space which rapidly equilibrates throughout the entire EC space. As contrast does not enter cells, this creates an osmotic disequilibrium between the IC and the EC (C). To achieve osmotic equilibrium 265 ml of water must move from the IC to the EC compartment. Thus a total of 365 ml have been added to the EC space, one third of which would be within the IV space.

We can use the osmolalities and amounts of the contrast agent used to estimate the increase in intravascular volume. For example, if 100 ml of a "high-osmolar" contrast with an osmolality of 1500 mOsm/l was administered intravascularly to a 70-kg patient, a total of 150 mOsm will be added to the body. If we assume the patient has a precontrast plasma osmolality of 300 mOsm/kg, and a precontrast total body water of 42 l (60% body weight), the new plasma osmolality after equilibration would be 12,750 mOsm/42.1 l or 302.8 mOsm/l. As the contrast media stays in the extracellular compartment (which originally was one-third of the total body water at 14 l) the total osmolarity in the extracellular space would now be 4200 + 150 = 4350 mOsm. To achieve a plasma osmolality of 302.8, this would require water movement from the intracellular space to the extracellular space and would require a new total extracellular fluid volume of 14,365 ml.

Thus, the administration of 100 ml of hyperosmolar contrast would move 265 ml of water from the intracellular compartment to the extracellular compartment, resulting in a total increase in the extracellular volume of 365 ml (Fig. 2). With only one-third of this extracellular compartment being intravascular, we would expect an increase in that space of only 120 ml. Even if we double the contrast load, this is a relatively insignificant amount of fluid and would not be expected to put the average patient at risk of acute fluid overload. The newer, more commonly used "low osmolar" contrast agents have osmolalities about one-half that of their high-osmolar counterparts and the fluid shifts would be equally reduced. I posit that that the concern over acute volume overload related to the use of radiocontrast agents in patients with CKD is highly exaggerated and the routine use of hemodialysis postcontrast for this reason is unnecessary.

Another concern related to contrast administration to patients with CKD is the effect of the contrast on remaining functional nephrons in patients whom are not anuric. Because contrast media is nephrotoxic, the patient with CKD (whether end-stage on dialysis or not) is at risk of acute damage (contrast-induced nephropathy) to those nephrons (4). In the patient with end-stage renal disease (ESRD), this may seem irrelevant as those patients are already receiving renal replacement therapy. However, as residual renal function plays a large role in ESRD patient outcome, especially those receiving peritoneal dialysis (PD) (5), its preservation in the dialysis patient is advantageous. In patients with CKD who are pre-ESRD, the advantages of avoiding further decreases in GFR are obvious.

The risk factors for contrast-induced nephropathy are well known and include contrast dose, contrast osmolality, and CKD, in addition to others (4). The increased risk in those patients with CKD is potentially explained by the increase in single-nephron glomerular filtration rate (GFR) and thus the filtered load of contrast per nephron. This would be akin to the administration of a larger dose of contrast to someone with a higher baseline GFR. Thus the administration of contrast media to patients with CKD provides a "double hit" to remaining functional

nephrons: an increased contrast load and prolonged tubular exposure.

Standard prophylactic measures to decrease to risk of contrast-induced nephropathy include the administration of intravenous fluids and *N*-acetylcysteine, both for a time period preceding and following contrast exposure (4). These measures may decrease the risk of contrast-induced nephropathy (thus maintaining residual renal function) in patients with CKD stages 2–4. However, no controlled trials examined these (or other) commonly used prophylactic measures in patients with ESRD.

The molecular weights of radiographic contrast media vary from 700 to 1550. They are minimally bound to serum proteins (3). These properties explain why the functional kidney easily clears contrast. In fact, the urinary clearance of a radioactive form of iothalamate (I^{125}), originally developed as an ionic radiocontrast agent in its nonradioactive form (MW 636), has often been used to measure GFR in clinical trials (6). These properties (low molecular weight and lack of protein binding) also make these agents excellent candidates for removal with hemodialysis or hemofiltration (HF).

As radiocontrast excretion is delayed in CKD, is there a role for hemodialysis or HF to speed up contrast elimination for patients with impaired renal function? Clearances of radiocontrast media with hemodialysis in patients with ESRD have been reported to range from approximately 100–150 ml/min, depending on the contrast and dialysis membrane (Table 1). The blood flow in each of these studies was a modest 200 ml/min. Even though the molecular weights of these molecules put them in the "middle molecule" category in which blood flow rate does not play an important role in clearance, these molecules are still relatively small and clearance has been shown to be enhanced with increases in the rate of blood flow (10). As contrast is limited to the extracellular space, the volume of distribution is relatively small. In addition, as contrast moves easily between the intravascular and interstitial compartments, dialytic removal of contrast should follow single pool kinetics. These factors would predict that a single dialysis treatment could remove significant quantities of contrast. Table 1 shows that a 4-hour hemodialysis treatment does in fact remove 70–80% of the administered contrast load, even with a conservative blood flow rate.

As hemodialysis is a reasonable means of removing radiocontrast in those with impaired renal function, is this procedure indicated? Let us first look at the nonrenal side effects of prolonged exposure to contrast in the patient with ESRD. There are a number of single case reports scattered across the literature that invoke contrast-related extrarenal side effects. One case involves a patient who developed skin biopsy-proven small vessel vasculitis that developed 48 hours after an intravenous pyelogram was performed using iohexol (11). However, the patient had a positive anti-nuclear antibody test and the study was carried out to evaluate renal insufficiency, most likely secondary to an autoimmune process in the first place. Another case describes a skin rash in an oliguric patient after high-dose urography thought related to iodine toxicity (12). There is one case of submandibular swelling (13), and four cases of "iodine mumps" (14) thought related to iodine exposure in patients with ESRD. In this report, two of the ESRD patients received iodine through the intake of an oral preparation for bronchitis, while the other two cases had recently received fistula arteriograms (15).

Three prospective studies attempted to determine whether exposure to contrast without postprocedure hemodialysis was harmful to patients with ESRD (16–18). Unfortunately the three studies involved a total of only 40 patients. All three studies utilized patients with ESRD maintained on thrice-weekly hemodialysis. The patients received contrast media for a scheduled study and were followed up for any possible side effects. None of the patients required dialysis before their next scheduled treatment and there were no more side effects than that seen in non-ESRD control groups receiving similar doses of contrast (16–18). Despite the limited number of patients studied, these reports lend support to the lack of extra-renal toxicity of contrast in patients maintained on hemodialysis. I have to believe that the paucity of reports of reactions to contrast in this very large population of patients in which contrast studies are commonly performed is even stronger evidence that extrarenal side effects from prolonged exposure to contrast are rare if they occur at all.

Hemodialysis postprocedure may also be used in an attempt to minimize damage to functional nephrons in patients with CKD regardless of whether they are receiving renal replacement therapy or not. While a number of studies have examined this, they involved only patients with CKD predialysis (19–25). Most of the trials were small, containing fewer than 20 patients per study arm, and not all were prospective or contained a control group. The authors reported the full spectrum of effect from benefit to harm. For example, one study reported 13

Table 1. Radiocontrast removal with hemodialysis

Contrast	MW[a]	Dialyzer membrane	QB[b] (ml/min)	Contrast clearance (ml/min)	Contrast removal at 4 hr	Reference
Ioversol	378	Cellulose acetate 2.1 m^2	200	130	82%	7
Iohexol	821	Cellulose diacetate 2.1 m^2	200	120	78%	8
Ioxaglate	1268	Cellulose diacetate 2.1 m^2	200	100	72%	8
Iopramide	791	Cupraphane 1.8 m^2	200	121	NA	9
		Polysulfone 1.8 m^2	200	162	NA	

[a]Molecular weight of contrast.
[b]Blood flow.

patients with CKD (creatinine 2.4–7.4 mg/dl) in which hemodialysis was provided to all the patients within 1.5–18 hours of contrast administration (19). The patients also received intravenous fluid prior to and after the contrast procedure but did not receive *N*-acetylcysteine. Creatinine levels remained stable in all patients for a 15-day period postcontrast. The authors concluded that dialysis was effective in preventing contrast-induced nephropathy, but this study had no control group.

Another study evaluated 30 patients with a mean creatinine of 2.4 mg/dl, one half of whom were randomized to start a 3-hour hemodialysis treatment within 60 minutes of contrast administration; the other half were not dialyzed (20). Both groups received normal saline at 83 ml/hr, which was initiated 12 hours before the contrast procedure. Neither group received *N*-acetylcysteine. Contrast-induced nephropathy was defined as an increase in serum creatinine of 0.5 mg/dl and did not differ between groups (53% on those receiving HD and 40% in the control group). The mean increase in creatinine in each group was also similar (0.7 mg/dl).

A third study involving 113 patients with CKD (mean creatinine 3.5 mg/dl) were randomized to either a 3-hour hemodialysis treatment or no hemodialysis postprocedure, with those being dialyzed receiving it within 30–180 minutes after contrast administration (median time 120 min) (21). Both groups received normal saline at 1 ml/kg/hr for 12 hours before and after the contrast procedure and neither group received *N*-acetylcysteine. The primary endpoint was the need for hemodialysis within 6 days after the contrast procedure and this occurred in eight patients in the hemodialysis arm of the study and in three patients in the control group ($p = 0.12$). In addition, after an initial decrease in the serum creatinine immediately following hemodialysis in the treatment group, the creatinine levels rose to higher levels than their baseline levels, while this did not occur in the control group. The authors suggested that hemodialysis postprocedure in patients with CKD might actually be harmful to the kidney.

These studies do not support postprocedure hemodialysis to prevent contrast-induced nephropathy in patients with impaired renal function. This is supported by a recent comprehensive review on this topic (26). Are these results surprising? Contrast is easily and effectively dialyzed. However, the unavoidable lag time from contrast administration to initiation of dialysis is not insignificant given how easily and quickly the native kidney filters the contrast material. Indeed, the kidneys' fate may be sealed within minutes after the contrast dose if acute vasoconstriction accompanying contrast administration is an important etiologic factor in the development of acute renal failure. The most likely explanation is that tubular toxicity has already occurred by the time hemodialysis can be practically administered.

Hemofiltration has also been studied to prevent contrast-induced nephropathy in patients with CKD. Two studies have been published by the same group of investigators (27,28). The first study (total $n = 114$, all receiving a coronary angiographic procedure, mean baseline creatinine 3.0 mg/dl) had two arms, one half receiving isovolemic HF at 1000 ml/hr and the other half receiving normal saline at 1 ml/kg/hr. Both groups started their respective treatments for 4–8 hours before the angiogram and were continued for 18–24 hours after the procedure. HF was temporarily discontinued during the angiographic procedure. The primary outcome was an increase in serum creatinine of more than 25% above baseline values obtained before initiation of HF. The primary outcome measure occurred in 5% of patients receiving HF and in 50% of those receiving saline. The authors concluded that periprocedure HF was effective in preventing contrast-induced nephropathy (27).

The study was inherently flawed however in that the outcome measure was affected by the treatment itself. HF lowered serum creatinine levels in those receiving it and thus any rise in the serum creatinine above baseline as a result of contrast-induced nephropathy would be attenuated by the serum creatinine level now being at a lower level than the original baseline value. The same group repeated the study in 92 patients randomized into three arms, IV hydration alone pre- and postcontrast, IV hydration precontrast followed by HF postcontrast, and HF alone pre- and postcontrast (28). The outcome measure was the same 25% increase in serum creatinine from baseline preintervention values. HF, when administered both pre- and postcontrast, had the best outcome but this study is similarly flawed because of the aforementioned problem.

The potential advantage of the HF approach would be in the lack of delay in the extracorporeal removal of contrast as HF was restarted immediately following the completion of the contrast procedure. It should be pointed out however that the contrast clearance rate achieved by HF at the rate of 1 l/hr (16.6 ml/min provided a maximal sieving coefficient for contrast across the HF membrane of 1.0) would be substantially less than that seen in standard hemodialysis (Table 1). This would also be the case for PD as a means of contrast removal. Both methods could potentially be started sooner than hemodialysis following contrast administration, but their low rates of clearance prolong tubular exposure to the contrast media and present a situation similar to hemodialysis in which the delay in starting the procedure increases exposure time of the contrast to the kidney. I therefore cannot recommend HF (or PD) as a postprocedure method of preventing contrast-induced nephropathy in patients with CKD.

I have attempted to debunk the myth that hemodialysis is routinely needed postprocedure in patients with CKD receiving intravascular radiocontrast. I felt it necessary to go into the details of many of the studies relating to this issue, as the need for postprocedure hemodialysis is often presented as "conventional wisdom" by the radiologist. I am certain that in some institutions this can be a contentious topic. However, I can only conclude that the opinions that support postprocedure hemodialysis have been based on rare case reports or poorly designed trials. Although contrast agents are hyperosmolar, their effect on intravascular volume should be clinically insignificant in most cases. Extrarenal side effects from prolonged exposure to contrast in patients with CKD are rare if they even exist at all. Although contrast media are well dialyzed, there is an unavoidable delay in starting that treatment after administration of contrast which may

obviate any benefit. Even if this were not the case, its utility in preventing contrast-induced nephropathy would remain quite uncertain. Therefore, there is currently no sound basis for routinely recommending hemodialysis (or HF) in patients at high risk for contrast media-associated complications. This is not to say that there are no situations where postprocedure hemodialysis may be appropriate. However, these must be uncommon and nephrologists should feel comfortable using their own best clinical judgment.

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