

Contrast Selection in the Cardiac Catheterization Lab

Does choice of contrast agent really matter?

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Since the first selective injection of contrast media into the right coronary artery by F. Mason Sones, MD, on October 30, 1958, there has been considerable refinement in contrast media. Multiple agents have been utilized and studied since the original data from Sones comparing meglumine iothalamate and sodium iothalamate to meglumine diatrizoate and sodium diatrizoate in 2,258 patients with and without cardiac disease.¹ With the introduction of multiple newer-generation contrast agents, the question arises, “Does contrast agent selection matter?” To adequately address this question, several issues must be considered. These include the effect of various contrast agents on incidence of renal toxicity and contrast-induced nephropathy (CIN), prothrombotic and anticoagulant properties *in vivo* that manifest as major cardiac events (MACE) and, with the emerging health care economic crisis, cost.

When considering an agent to visualize vascular structures, there are many different properties to keep in mind; the major properties are viscosity, ionic versus nonionic, and osmolality. The osmolality depends on the number of molecules that are present in the solution, which can be reduced by producing agents that do not dissociate (non-

ionic) or by production of dimeric molecules. Numerous studies, including a meta-analysis of 31 trials, have shown low-osmolar contrast media (LOCM) to be associated with significantly less CIN than high-osmolar contrast media in patients with renal impairment and/or diabetes.² There has been considerable refinement during the past decades from ionic high-osmolar, to nonionic low-osmolar, and finally to nonionic iso-osmolar contrast media (IOM). High-osmolar agents have concentrations >2,000 mOsm/kg H₂O, whereas LOCM are in the range of 600 mOsm/kg H₂O to 844 mOsm/kg H₂O. Blood has an osmolality of 290 mOsm/kg H₂O and, therefore, an “isomolar” agent has an osmolality the same as blood. LOCM that are nonionic agents include iohexol, iopamidol, iopentol, iopromide, imeprol, iobitridol, and ioversol. The sole LOCM ionic dimmer available is ioxaglate.³ The only currently available iso-osmolar agent is iodixanol.

NEPHROTOXICITY

Several studies have evaluated the incidence of CIN comparing LOCM to IOM (Table 1). Aspelin et al⁴ conducted a randomized, double-blind, prospective, multicenter study in 129 patients undergoing coronary or

TABLE 1. MAJOR TRIALS OF NEPHROTOXICITY

Study	Agents Used	Patient Population	Endpoints	Results
Jo et al ⁵ RECOVER	Iodixanol and ioxaglate	300 CrCl <60 mL/min	Increase in serum creatine ≥25% or ≥0.5 mg/dL	IOM superior
Aspelin et al ⁴ NEPHRIC	Iohexol and iodixanol	129 patients with dimeric molecules and SCr 1.5–3.5	Increase in serum creatine ≥25% or ≥0.5 mg/dL	IOM superior
Solomon et al ⁷ CARE	Iopamidol and iodixanol	414	Serum creatine increase ≥0.5	No significant difference
Liss et al ¹⁰ Registry	Iodixanol (iso-osmolar) and ioxaglate (low-osmolar)	57,000	Rehospitalization with renal failure or hemodialysis	LOCM superior

aortofemoral angiography comparing the nephrotoxic effects of iodixanol with those of iohexol. This study (NEPHRIC) involved 129 patients with diabetes with serum creatinine concentrations of 1.5 to 3.5 mg/dL. The primary endpoint was the peak increase from baseline in the creatinine concentration during the first 3 days after angiography. The creatinine concentration increased significantly less in patients who received iodixanol. From day 0 to day 3, the mean peak increase in creatinine was 0.13 mg/dL in the iodixanol group and 0.55 mg/dL in the iohexol group ($P=.001$). These investigators concluded that CIN may be less likely to develop in high-risk patients when iodixanol is used rather than a nonionic LOCM.⁴

Jo et al⁵ compared the renal tolerance of the LOCM ioxaglate (Hexabrix, Covidien, Hazelwood, MO) and iodixanol (Visipaque, GE Healthcare, Waukesha, WI) in The Renal Toxicity Evaluation and Comparison between Visipaque (iodixanol) and Hexabrix (ioxaglate) in Patients with Renal Insufficiency Undergoing Coronary Angiography (RECOVER) study. This was a prospective, randomized trial of 300 patients with creatinine clearance of <60 mL/min. The primary endpoint was the incidence of CIN defined as an increase in serum creatinine $\geq 25\%$ or ≥ 0.5 mg/dL. The incidence of CIN in patients with severe renal impairment at baseline ($\text{CrCl} < 30$ mL/min) or diabetes and in those receiving large doses (≥ 140 mL) of contrast medium was also determined. The incidence of CIN was determined to be significantly lower with iodixanol (7.9%) than with ioxaglate (17%; $P=.021$). The incidence of CIN was also significantly lower with iodixanol in patients with severe renal impairment ($P=.023$) or concomitant diabetes ($P=.041$), or in patients receiving ≥ 140 mL of contrast media ($P=.038$).⁵ These findings are further supported by McCullough et al in a recent meta-analysis of 2,727 patients, indicating that the use of IOCM is associated with smaller increases in creatinine and lower rates of CIN than LOCM, especially in patients with chronic kidney disease and diabetes.⁶

In contrast, Solomon et al⁷ compared the incidence of CIN between the LOCM iopamidol with that of the IOCM iodixanol in the Cardiac Angiography in Renally Impaired Patients (CARE) study. This was a multicenter, randomized, double-blind trial that compared the renal tolerability of 414 high-risk patients (defined as having a glomerular filtration rate of 20 to 59 mL/min) undergoing cardiac angiography or percutaneous coronary intervention (PCI). The primary endpoint was defined as a serum creatinine increase ≥ 0.5 mg/dL over baseline at 2 to 5 days. Mean postprocedure serum creatinine increases were significantly less with iopamidol ($P=.01$). The investigators determined that the rate of CIN is not statistically different after the intra-arterial administration of iopami-

dol or iodixanol to high-risk patients, with or without diabetes mellitus, and iopamidol was associated with a significantly smaller mean increase in serum creatinine levels when compared with iodixanol.⁷ Similarly, Barrett et al² compared the effects on renal function of iopamidol and iodixanol in a multicenter, double-blind, randomized trial of 166 patients with chronic kidney disease defined as serum creatinine ≥ 1.5 mg/dL and/or creatinine clearance ≤ 60 mL/min undergoing contrast-enhanced multidetector CT. An absolute increase ≥ 0.5 mg/dL in creatinine clearance was observed in none of the patients receiving iopamidol-370 and in 2.6% (2/76) of patients receiving iodixanol-320 ($P=.2$). These investigators concluded that the rate of CIN was similarly low in patients with stable moderate-to-severe chronic kidney disease after intravenous administration of iopamidol-370 or iodixanol-320 for CT.⁸ This being stated, there may be differences in effects of intravenous versus intra-arterial contrast effects on nephrotoxicity.

These findings were further supported at a 2006 oral presentation of the Ionic Versus Nonionic Contrast to Obviate Worsening of Nephropathy After Angioplasty in Chronic Renal Failure Patients (ICON) trial.⁹ This cohort of 145 patients with renal insufficiency undergoing angiography was randomized to receive ioxaglate and iodixanol. All patients had chronic kidney disease with serum creatinine measurements from 1.5 to 3 mg/dL. All subjects were well hydrated, receiving approximately 3.7 L of fluid. The use of N-acetyl-cysteine was left to the discretion of the investigator. The primary endpoint was the peak increase in serum creatinine out to day 3. Compared with ioxaglate, iodixanol did not significantly reduce the increase in serum creatinine levels after coronary catheterization or PCI. There was no significant difference between the two agents at any time, nor was there any difference between the two agents when other definitions of contrast nephropathy were used. Furthermore, in-hospital and 30-day outcomes did not differ between the two agents.⁹ The ICON trial has not been peer reviewed or published, however.

Finally, Liss et al¹⁰ compared the Swedish Coronary Angiography and Angioplasty Registry with the Swedish Hospital Discharge Register to assess contrast media-induced renal failure. Data from 23 hospitals, including more than 57,000 patients, were analyzed. From 2000 to 2003, iodixanol (iso-osmolar) was used in 45,485 patients, and ioxaglate (low-osmolar) was used in 12,440 subjects. To include the earlier used contrast media iohexol (low-osmolar), analysis extended back to 1990 (86,334 patients). Renal toxicity was defined by rehospitalization with renal failure or by requiring dialysis. Using these definitions, the incidence of clinically significant renal failure was

greatest for patients receiving the IOCM iodixanol (1.7%). Ioxaglate-treated patients had a significantly lower renal failure incidence (0.8%; $P<.001$). The odds ratio for iodixanol-treated patients was significantly higher than for ioxaglate (1 vs 0.48; $P<.001$). In subsets of either diabetic patients or patients with previous renal failure, the odds ratios for renal failure remained greater in the iodixanol groups ($P<.01$). Hospitals switching contrast media to iodixanol experienced a doubling in clinically significant renal failure after cardiac procedures. Dialysis was required in 0.2% of patients receiving iodixanol, which was significantly higher ($P<.01$) than for ioxaglate-treated patients (0.1%). Iohexol-treated patients had a similar low risk for developing clinically significant renal failure (0.9%) as ioxaglate-treated patients. The investigators concluded that the risk of developing clinically significant renal failure and required dialysis after coronary procedures is higher when patients received iodixanol rather than ioxaglate or iohexol.¹⁰ The data presented from this study are retrospective and therefore could be subject to bias (ie, more liberal use of contrast in patients receiving iodixanol due to perceived greater safety). These factors cannot be excluded. However, the investigators do acknowledge this fact, and for the 1 year that volumes were recorded, the amounts were found to be similar.

MACE

Previous *in vitro* and *in vivo* studies have suggested an association between thrombus-related events and type of contrast media (Table 2). Davidson et al performed a multicenter, prospective, randomized, double-blind trial in 856 high-risk patients undergoing coronary artery intervention comparing iodixanol with ioxaglate in the COntRast media Utilization in high-Risk PTCA (COURT) trial.¹¹ High risk was defined as rest angina within 48 hours, evolving myocardial infarction (MI) within 72 hours, or after MI ischemia within 2 weeks. The primary endpoint was in-hospital MACE. A secondary objective was to evaluate major angiographic and procedural events during and after PTCA. The composite in-hospital primary endpoint was less frequent in those receiving iodixanol compared with those receiving ioxaglate (5.4% vs 9.5%, respectively; $P=.027$). Core laboratory-defined angiographic success was more frequent in patients receiving iodixanol (92.2% vs 85.9% for ioxaglate; $P=.004$). There was a trend toward lower total clinical events at 30 days in patients randomized to iodixanol (9.1% vs 13.2% for ioxaglate; $P=.07$). The iodixanol cohort experienced a 45% reduction of in-hospital MACE when compared with the cohort receiving ioxaglate; however, in-hospital car-

TABLE 2. MAJOR TRIALS OF MACE

Study	Agents Used	Endpoints
Davidson et al COURT ¹¹	Iodixanol and ioxaglate	Iodixanol reduction in MACE
Harrison et al ¹²	Iodixanol and iopamidol	Iodixanol reduction in MACE
Le Feuvre et al ¹³	Ioxaglate and iodixanol	Ioxaglate reduction in MACE
Sutton et al ¹⁴	Ioxaglate and iodixanol	Trend favoring ioxaglate

diac death was higher in the iodixanol cohort (5 vs 1; $P=.1$). Similarly, Harrison et al evaluated 1,276 patients in a randomized, double-blind, multicenter trial comparing iodixanol to iopamidol. In this study, patients receiving iodixanol had lower in-hospital MACE rates compared to iopamidol, driven by lower rates of non-Q-wave MIs.¹²

In contrast, Le Feuvre et al¹³ evaluated iodixanol or ioxaglate in a prospective single-center study of 498 consecutive patients. The primary endpoint was the cumulative rate of in-hospital MACE. A secondary endpoint was the rate of angiographic or procedural complications. In-hospital MACE was more frequent in patients receiving iodixanol compared with patients receiving ioxaglate (4.8% vs 0.3%; $P<.005$). This difference was mainly related to the appearance of a large thrombus during PCI (6% with iodixanol vs 0.3% with ioxaglate; $P<.0001$). The investigators concluded that thrombus-related events are more frequent with iodixanol than with ioxaglate.¹³ Further evidence of a beneficial effect of ionic LOCM was demonstrated by Sutton et al.¹⁴ This group published results from a randomized, prospective, double-blind trial comparing ioxaglate to iodixanol in 618 patients undergoing PCI for stable or unstable coronary artery syndromes. The incidence of the combined primary endpoint (failed catheter laboratory outcome, bailout stenting, or abciximab, MI, or death before hospital discharge) was higher in the iodixanol group compared to the ioxaglate group (17.9% vs 14.8%), although this did not reach statistical significance ($P=.29$). In patients with an acute coronary syndrome, there was a trend toward a reduced incidence of the combined endpoint in the ioxaglate compared to the iodixanol group, although this did not reach statistical significance (17.2% vs 24.8%; $P=.17$). The investigators concluded that there is no clear advantage with the use of an ionic contrast agent in a large population of patients undergoing PCI for both stable and unstable coronary artery disease. They do state, however, that the possibility remains that ionic agents do have advantages for patients with unstable coronary artery disease undergoing PCI.¹⁴

EFFECTS ON THROMBOSIS, PLATELET ACTIVATION, AND INFLAMMATION

Several explanations for the differential clinical outcomes listed previously may be explained by varying effects of contrast media on platelet activation, thrombosis, and inflammation. LOCM are generally found to be anticoagulant *in vitro*, with ionic contrast media having a greater anticoagulant effect than the nonionic agents. Jung et al evaluated the effects of ionic (ioxaglate) and nonionic (iopromide) contrast media on hemostatic parameters in 40 patients undergoing coronary angiography. The investigators concluded that the use of an ionic contrast media (ioxaglate) in diagnostic cardiac catheterization angiography is associated with lower thrombin generation and lower activation of the platelet system than when a non-ionic contrast media (iopromide) is used.¹⁵

Jones and Goodall investigated the effect of iohexol, iodixanol, and ioxaglate on thrombus formation and fibrinolysis *in vitro*. They found that thrombi formed with iodixanol or iohexol were larger and more resistant to thrombolysis, whereas ioxaglate may reduce the risk of thrombus formation.¹⁶ Iodixanol and ioxaglate did not increase platelet degranulation, but iohexol caused a significant increase compared to the saline control. Furthermore, Al Dierri et al have demonstrated ioxaglate to be a potent inhibitor of thrombin in plasma, to potentiate platelet inhibition of abciximab, and to have an additive effect with heparin.¹⁷ Laskey and Gellman compared the effects of the nonionic agents iohexol and iodixanol to ioxaglate in 37 patients undergoing angiography and determined an associated increase in the inflammatory markers IL-6 and TNF- α with all three agents. This increase however, was less with the nonionic agents.¹⁸

CONCLUSION

It appears that the choice of contrast agent plays a seemingly small role in the development of CIN or MACE. In patients with diabetes and/or chronic kidney disease, there may be a decrease in the postprocedural rise in creatinine with the use of the iso-osmolar agent iodixanol compared to LOCM. It is unclear if this benefit translates into clinical outcomes, such as rehospitalization for renal failure or requiring hemodialysis, which actually favored the use of LOCM from registry data. The data regarding MACE are even more conflicting. An emerging body of evidence would support the use of the ionic LOCM agent ioxaglate in patients with unstable coronary syndromes giving its potential favorable antithrombogenic properties; however, the data regarding clinical outcomes are conflicting. Therefore, we believe the most important measures to prevent complications include careful upstream preventative measures (intravenous hydration), as well as contrast-

sparing techniques (use of biplane) in avoiding nephrotoxicity and close attention to antiplatelet therapy in reducing MACE. Economic analysis is beyond the scope of this review; however, given the emerging constraints on cost, we predominantly favor the use of the less-expensive LOCM in our lab. ■

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