

Editöryal Yorum / Kontrast nefropatisi

Editorial / Contrast-induced nephropathy

Dr. Sinan Aydoğdu

Contrast-induced nephropathy has been defined as acute renal damage developed secondary to intravenous contrast agents in interventions performed for diagnostic, and therapeutic purposes. It is responsible for nearly 10-15 % of hospitalizations because of acute renal failure (ARF).^[1] When other causes of ARF are ruled out, it is defined as a relative increase of ≥ 25 % in serum creatinine levels above baseline values or an absolute increase of $\geq 0,5$ mg/dl. Serum creatinine level begins to rise within 24-48 hours after administration of contrast agent, and reaches to peak values after 3-5 days. Renal failure is more frequently of non-oliguric type. Mostly, serum creatinine value drops to normal levels within 1-3 weeks. However, sometimes these levels do not return to baseline values, and can progress to irreversible renal dysfunction. Although in most of the cases permanent damage does not occur, studies have demonstrated that contrast-induced nephropathy leads to increases in hospital stay, healthcare expenditures, incidence of morbidity, and mortality.^[2-4] Although pathophysiology of contrast-induced nephropathy is not completely known, vasoconstriction of renal vessels, oxidative stress, free radical damage, and endothelial dysfunction are thought to be culprit factors. Risk factors of contrast-induced nephropathy can be analyzed in two groups as: 1-Patient-related risk factors, 2- Risk factors related to the contrast agent

Patient-related risk factors consist of diminished glomerular filtration rate (≤ 60 ml/min), diabetic nephropathy, congestive

heart failure, dehydration, advanced age, concomitant use of nephrotoxic drugs (especially, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, loop diuretics, and metformin). Risk factors related to contrast agent are use of agents with higher osmolarity, and excess amounts of contrast agent.[5,6]

Intravenous contrast agent used in diagnostic, and therapeutic procedures can be analyzed in three main headings:

1- High-osmolarity contrast agents : They are first-generation radiocontrast agents. They contain sodium salts of meglumine, and diatrizoic acid with high osmolarity . They are hypertonic solutions, and their osmolarity is nearly 5 times of plasma osmolarity (nearly 1400-1800 mOsmol/kg). They are not in use anymore because of their adverse effects.

2- Low-osmolarity contrast agents: Their osmolarities range between 600, and 1000 mOsmol/kg. They are categorized in two groups as non-ionic monomers, and ionic dimers.

3-Iso-osmolar contrast agents: They are third-generation radiocontrast agents. Their osmolarities range between 280, and 290 mOsmol/kg. They provide better imaging quality with a more favourable side effect profile. However their higher viscosity is their unfavourable characteristic feature.

Osmolarity of the contrast agent is as important as its amount used. One of the most important factors in the prevention of contrast-induced nephropathy is limitation of the contrast agent at most to 100 mg per dose.

Yazışma adresi: Dr. Sinan Aydoğdu. Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, 06230 Ankara.

Tel: 0312 - 306 10 00 e-mail: sinanaydogdu@yahoo.com

Address of correspondence: Clinics of Cardiology, Turkey Higher Specialization Training and Research Hospital, 06230 Ankara

Phone: : 0312 - 306 10 00 e-mail: sinanaydogdu@yahoo.com

Many studies have been conducted to curtail contrast-induced nephropathy using various measures such as hydration, antioxidant, and vasodilator drugs. Only hydration has demonstrated clear-cut effectiveness. However, hydration can not only prevent development of nephropathy in patients with normal renal function, but also decreases the risk of contrast-induced nephropathy in patients with GFRs less than 60 mg/dl.^[7]

Many investigations have demonstrated that high-osmolarity contrast agents have a significantly higher probability of inducing nephropathy when compared with hypo- and iso-osmolar agents [8,9] However, whether iso-osmolar agents are different from hyposmolar agents is still a subject of debate. Its most important reason is different diagnostic criteria of contrast-induced nephropathy used in various studies. Earlier studies had reported lower risk of nephrotoxicity for iso-osmolar dimeric contrast agent iodixanol relative to low-osmolarity monomeric radiocontrast agents.^[10] However more recent studies have not supported this thesis. Nearly identical rates of contrast nephropathy have been reported for iso-osmolar, and low-osmolarity agents.^[11-13] Similarly, in a study [14] published in 2012 in *The American Journal of Cardiology*, Bolognese et al reported that hypo-, and iso-osmolar contrast agents induce similar rates of contrast nephropathy

The most important reason why dimeric iso-osmolar agents have lower risk of nephropathy than low-osmolarity agents has been associated with higher viscosity of dimeric iso-osmolar agents, and hyperviscosity was thought to induce nephrotoxicity. However further supportive studies should be performed on this thesis.

In line with outcomes of investigations, and meta-analyses which have not supported the thesis of relatively lower nephrotoxicity of iso-osmolar agents, in the guidelines (ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline) jointly published by American College of Cardiology Foundation and American Heart Association, the statement stating “iso-osmolar agents should be preferred

in chronic renal failure” was withdrawn from the guidelines.

In a study by Gül et al which was published in your periodical of *Archives of the Turkish Journal of Cardiology* [2013; 41:21-7] iso-osmolar contrast agent iodixanol, and hypoosmolar iopamidol were compared as for their risk of nephropathy in patients who had had coronary angiography with the indication of acute coronary syndrome. Their outcomes are in accordance with those of the recent relevant publications, and meta-analyses. Gül et al reported that any difference could not be found between iodixanol, and iopamidol groups as for induction of nephropathy. However, as they stated in their article, scarcity of the number of patients in the iso-osmolar contrast agent group might effect their results. Besides, diagnosis of contrast-induced nephropathy was made based on the peak value of serum creatinine values measured within a period of 72 hours. However, in the studies cited in the medical literature which advocated that iso-osmolar agents had conveyed lower risk of nephropathy, serum creatinine levels had been evaluated for 24-48 hours. Since the study by Gül et al. encompassed a longer period of time (72 hrs) which might influence their outcomes more favourably. Perhaps, measurement of creatinine levels for 3-5 days might confirm the diagnosis of contrast-induced nephropathy more affirmatively with better standardization of comparison criteria of these two contrast agents. Another remarkable feature of the study is that all patients received hydration therapy. However, as indicated by the authors in the references, the beneficial effects of hydration were only reported in patients .with renal dysfunction. Therefore, for the time being, hydration therapy is not indicated for all patients. When comparing baseline characteristics of the patients, grouping, and evaluation of the patients according to their glomerular filtration rates (i.e. GFR <60 ml/min and 60-90 ml/min, and normal renal function) would identify the patient group who would be minimally affected by the deleterious effects of the contrast agent. Besides, longer follow-up periods (i.e. one-month follow up of serum creatinine levels) of the patients would provide more information about the patient group who would develop permanent renal dysfunction because of contrast-induced nephropathy.

In conclusion, the most important factor in the prevention of contrast-induced nephropathy is to keep the amount of contrast agent used at a minimum level. Both osmolality, and viscosity of the contrast agents should be taken into consideration in the preferences of the physicians. Maintenance of adequate hydration in patients with renal dysfunction will help to prevent contrast-induced nephropathy.

Conflict of interest: None declared

REFERENCES

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983;74:243-8.
2. Weisbord SD, Palevsky PM. Radiocontrast-induced acute renal failure. *J Intensive Care Med* 2005;20:63-75.
3. Dargas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol* 2005;95(1):13-9.
4. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 2006;11-5.
5. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S, et al. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 2004;93:1515-9.
6. Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 2006;100:S11-5.
7. Pannu N, Wiebe N, Tonelli M; Alberta Kidney Disease Network. Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006;295:2765-79.
8. Moore RD, Steinberg EP, Powe NR, Brinker JA, Fishman EK, Graziano S, et al. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. *Radiology* 1992;182:649-55.
9. Lautin EM, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, et al. Radiocontrast-associated renal dysfunction: a comparison of lower-osmolality and conventional high-osmolality contrast media. *AJR Am J Roentgenol* 1991;157:59-65.
10. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ; Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;348:491-9.
11. Kanei Y, Ayabe K, Ratcliffe J, Vales L, Nakra N, Friedman P, et al. The impact of iso-osmolar contrast use in emergent percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Invasive Cardiol* 2011;23:448-50.
12. Laskey W, Aspelin P, Davidson C, Rudnick M, Aubry P, Kumar S, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. *Am Heart J* 2009;158:822-828.e3.
13. Serafin Z, Karolkiewicz M, Gruszka M, Stróżecki P, Lasek W, Odrowaz-Sypniewska G, et al. High incidence of nephropathy in neurosurgical patients after intra-arterial administration of low-osmolar and iso-osmolar contrast media. *Acta Radiol* 2011;52:422-9.
14. Bolognese L, Falsini G, Schwenke C, Grotti S, Limbruno U, Liistro F, et al. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). *Am J Cardiol* 2012;109:67-74.
15. Gül M, Turan B, Uğur M, Türer A, Fındıkçıoğlu U, Ergelen M, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with acute coronary syndrome. [Article in Turkish] *Türk Kardiyol Dern Ars* 2013;41:21-7.

Anahtar sözcükler: Böbrek hastalıkları; diyabetik nefropati/komplikasyon; koroner anjiyografi; kontrast maddesi; kreatinin/kan; ozmolar konsantrasyon.

Key words: Kidney diseases; diabetic nephropathy/complications; coronary angiography; contrast media; creatinine/blood; osmolar concentration.