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# Comparing the Renal Safety of Isoosmolar Versus Low-Osmolar Contrast Medium by Renal Biomarkers *N*-Acetyl-β-D-Glucosaminidase and Endothelin

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## Abstract

Iodixanol and iopamidol are commonly used contrast agents in coronary angiography. We evaluated the nephrotoxic effects of both contrast media in relation to renal biomarkers. A total of 38 low-risk patients who underwent coronary angiography were enrolled. Patients were randomized to receive either low-osmolar nonionic monomer or isoosmolar nonionic dimer contrast medium. *N*-Acetyl-β-D-glucosaminidase (NAG), endothelin, blood urea nitrogen, and urine and serum creatinine (SCr) levels were measured before the procedure (T0), at 6 hours (T6), and at 1 year after the procedure. Plasma endothelin, urine NAG/creatinine, and SCr were higher; accordingly, the urine creatinine values were lower in both the groups when comparing T0 versus T6. The groups were similar with each other when comparing T0 and T6 values. Both the contrast agents may be safely used at a low volume for coronary angiography in low-risk patients. Endothelin and NAG are sensitive to acute renal changes in function. There is a need for further prospective investigations with more patients.

## Keywords

contrast agents, contrast-induced nephropathy, coronary angiography, endothelins

## Introduction

Diagnostic and therapeutic contrast media-based procedures are increasingly carried out.[1] However, there may be an increased risk of contrast-induced nephropathy (CIN). Radiocontrast materials may have nephrotoxic effects,[2] especially in the presence of risk factors such as diabetes mellitus (DM), congestive heart failure, old age (>70 years), and most importantly preexisting renal failure.[3]

The physiopathology of CIN is multifactorial and complex. A contrast agent may potentiate renal injury via oxidative stress, free radical damage, and endothelial dysfunction.[3,4] Contrast medium induced release of endogenous vasoconstrictor (eg, endothelin) leads to a decrease in renal blood flow and an increase in free radical formation.[2,5-7] Elevated endothelin levels were detected in plasma and urine in patients with CIN.[7] High plasma endothelin levels in rats 2 hours after radiocontrast agent infusion have been reported.[8]

*N*-Acetyl-β-D-glucosaminidase (NAG), a proximal tubular lysosomal enzyme, rises in urine as an early indicator of proximal tubular cell necrosis before serum creatinine (SCr).[9] The diagnosis of nephrotoxicity requires longer term follow-up of SCr, blood urea nitrogen (BUN), and creatinine clearance which increases the length of hospital stay and costs.[10] The determination the nonoliguric increase in SCr level needs at least 48 hours of asymptomatic period and this increase has to be maintained for 2 to 5 days; thus, this does not provide an early diagnosis of CIN.[11] Also, the SCr levels are influenced by age, gender, nutrition, and body composition and are not increased until the glomerular filtration rate is reduced by up to 50%.[3]

Once renal dysfunction occurs after contrast media administration, the risk of death increases and this requires long-term

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follow-up. Zhang et al demonstrated the effect of iodinated contrast media iopamidol-370 on renal hemodynamics and oxygenation which was associated with an early decrease (at 1 hour) in renal blood flow that reached its minimum at 24 hours and returned to baseline by 48 hours.[12] In another experimental study, iodixanol induced renal hypoperfusion significantly at 16 minutes.[13]

Because of their lower nephrotoxic effects, isoosmolar contrast agents are considered more convenient than high-osmolar agents. Low-osmolar contrast agents are safer than high-osmolar contrast media, and isoosmolar ones are recommended as being less nephrotoxic in patients with reduced renal function. However, in Japan, isoosmolar agents are not approved for coronary angiography.[7] Therefore, in studies, there is an increasing trend searching for early markers of renal injury and safer radiocontrast agents especially for high-risk patients.[14]

In the present study, we compared the renal effects of the nonionic, isoosmolar agent, iodixanol versus the nonionic, low-osmolar agent, iopamidol with renal biomarkers NAG and endothelin in patients with normal renal function undergoing coronary angiographic procedures.

## Materials and Methods

### Study Design and Participants

This prospective, randomized, parallel group comparison study was conducted with 44 patients in the Department of Cardiology, at Ataturk Training Hospital from June 2009 to December 2010. In all, 6 patients lost to follow-up and excluded.

All consecutive hospitalized adult patients, 20 years of age or older, with normal renal function (SCr <1.4 mg/dL) who had stable angina pectoris or suspected coronary artery disease and who were referred for coronary angiography were enrolled. All patients undergoing coronary angiography were randomized to receive either low-osmolar nonionic monomer (Iopamidol-Iopamiro, Isovue, Solutrast, Bracco Diagnostics, Italy) or isoosmolar nonionic dimer contrast medium (iodixanol-Visipaque, GE Healthcare, Princeton, New Jersey). Demographic and clinical characteristics are listed in Table 1.

Exclusion criteria were acute myocardial infarction, unstable SCr levels, renal insufficiency, history of percutaneous transluminal coronary angioplasty or coronary bypass surgery, congestive heart failure or ejection fraction <45%, current pregnancy, or other medical conditions that would decrease the chance of obtaining reliable data (eg, uncontrolled hypertension, cardiomyopathy or cardiac valve disease, systemic inflammatory disease, decompensated renal, hepatic, cardiac, endocrine disorders, clinical laboratory evidence of infection, recent exposure to contrast media within 2 days of study entry, and administration of dopamine, mannitol, or diuretics).

Patients with fasting glucose ≥126 mg/dL or those under diabetic treatment were defined as having abnormal glucose tolerance. Patients with systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥85 mmHg or patients treated with antihypertensives were defined as having hypertension. A body mass index (BMI) ≥30 kg/m$^2$ was defined as overweight. Current smokers were defined as those who had smoked at least for a period of 1 year and smoked at present.

**Table 1.** Clinical and Demographic Characteristics at Baseline Between the 2 Groups.[a]

| | Group 1 (n = 19; Iopamidol) | Group 2 (n = 19; Iodixanol) | *P* |
|---|---|---|---|
| Median age, years | 60 (38-75) | 56 (40-70) | .111 |
| Gender, M/F | 10/9 | 16/3 | .079 |
| EF, % | 67 | 60 | .745 |
| Contrast volume, mL | 52 (47-62) | 52 (48-62) | .587 |
| Hypertension, % | 13 (68.4) | 9 (47.4) | .325 |
| Diabetes mellitus, % | 8 (42.1) | 3 (15.8) | .151 |
| Hyperlipidemia | 8 (42.1) | 4 (21.1) | .295 |
| Smoking status, % | 8 (42.1) | 13 (68.4) | .191 |
| BMI, ≥30 | 7 (36.8) | 6 (31.6) | .531 |

Abbreviations: BMI, body mass index; F, female; EF, ejection fraction; M, male.
[a] Data presented as median (range). Categorical data presented as n (%). Mann-Whitney *U* test was used for continuous variables. Fisher exact test was applied for categorical variables.

The SCr, BUN, plasma endothelin, urine NAG, and urine creatinine were measured at baseline and 6 hours after the procedure (ie, after contrast media administration). Renal function was evaluated for CIN by SCr assays at 6 hours and 1 year after angiography.

The study was approved by the Ethics committee of the hospital. The study was performed in accordance with the Declaration of Helsinki on human experimentation. All patients were informed and signed the consent forms before enrolment in the study.

### Coronary Angiography

Selective coronary angiography was performed by the interventional cardiologists by standard Judkins technique. The patients were iodinated with an average of 52 mL of contrast medium intra-arterially. All the diabetic patients received isotonic (0.9%) saline intravenously at a rate of 1 mL/kg per h for 6 to 12 hours before and after the angiography with combination of oral *N*-acetylcysteine (NAC) 600 mg administration twice daily. The angiogram picture was reviewed by 3 observers blinded to the clinical information.

### Blood Collection

The SCr was measured twice at 12 to 24 hours before the procedure and at 6 hours once and at 1 year after coronary angiography. Plasma endothelin and urine NAG were measured before and at 6 hours after the procedure. Evacuated tubes (Vacuette, Greiner Bio-One, Kremsmünster, Austria) were used to obtain serum (8 mL Vacuette Tube Serum Gel Separator); 4 mL tubes containing 3.2% sodium citrate were used to obtain plasma.

To avoid possible hemolysis, all tubes were allowed to stand for 30 minutes at room temperature, then centrifuged at 3000

rpm for 10 minutes at room temperature (according to the instructions of the tube manufacturer). All samples were free of hemolysis, lipemia, and hyperbilirubinemia visually. Aliquots of each sample were transferred into Eppendorf tubes and kept frozen at −80°C until analysis.

### Urine Collection

Fresh urine samples were collected from each participant precontrast (before any volume supplementation) for baseline values and at 6 hours after contrast administration. All were kept frozen at −80°C until analysis.

### Laboratory Testing

All aliquots containing serum and urine samples were thawed at the same time at room temperature. Endothelin, creatinine, and BUN were analyzed from plasma and serum samples; NAG and creatinine were analyzed from urine samples.

### Renal Function Markers

*Endothelin.* Plasma endothelin assay was performed with solid phase sandwich enzyme-linked immunosorbent assay on BioTek semiautomatic microplate reader (BioTek Instruments, USA) using Endothelin EIA kit (Cayman Chem. Comp. Michigan; Lot No: 177113). Intraassay and interassay coefficients of variation (CVs) were 5.02% and 8.10%, respectively. The detection limit was 0 to 250 pg/mL.

*N-acetyl-β-D-Glucosaminidase.* Urinary NAG activity was measured by a colorimetric assay on the Abbott Architect (Abbott, Wiesbaden, Germany) using NAG reagent (lot no: NG00207-3) from Diazyme lab (California). The results were expressed as U/L and were normalized to urinary creatinine values and expressed in mU/mg. Within-day and between-day CV's were 1.39% and 4.84%, respectively.

*The BUN, Serum, and Urine Creatinine.* The BUN was measured by the urease method. Creatinine was measured by the alkaline picrate method on the Abbott Architect with original reagents and with 2 levels of quality control materials (Bio-Rad Laboratories, Milano, Italy). The intraassay and interassay variabilities were <5%.

### Statistical Analysis

The baseline demographic and clinical characteristics were compared using Fisher exact test or Mann-Whitney *U* test, as appropriate (Table 1).

Postcontrast changes in plasma endothelin, urine NAG/creatinine, serum BUN, and creatinine were summarized as medians. The changes in the concentration of those variables were analyzed using nonparametric Friedman test for repeated measures. A $P$ value < .05 (2-tailed) was considered significant. The Wilcoxon signed-rank test was used for follow-up tests to evaluate the comparisons between pairs of medians after obtaining a significant Friedman test.

**Table 2.** Postdose Changes in Variables (T0: Baseline, T6: 6 Hours Postdose).[a]

| Variable | Iopamidol (Group 1) | Iodixanol (Group 2) | *P* |
|---|---|---|---|
| Plasma endothelin, pg/mL | | | |
| T0 | 6.45 (0.64-11.30) | 6.45 (0.64-24.80) | .680[b] |
| T6 | 7.42 (0.64-17.11) | 7.42 (2.26-33.50) | .646 |
| *P* | **.001**[c] | **.002** | |
| Urine creatinine, mg/dL | | | |
| T0 | 146 (24-282) | 135 (48-269) | .715 |
| T6 | 87 (21-180) | 57 (12-263) | .274 |
| *P* | **.001** | **.000** | |
| Urine NAG/Cr, U/mg | | | |
| T0 | 0.0075 (0.00-0.04) | 0.0073 (0.00-0.02) | .965 |
| T6 | 0.0116 (0.01-0.05) | 0.0163 (0.00-0.08) | .300 |
| *P* | **.000** | **.001** | |
| Serum creatinine, mg/dL | | | |
| T0 | 0.71 (0.57-1.40) | 0.77 (0.50-1.00) | .501 |
| T6 | 0.79 (0.66-1.53) | 0.82 (0.54-1.03) | .826 |
| *P* | **.011** | .157 | |
| BUN, mg/dL | | | |
| T0 | 16.0 (9-29) | 14.0 (7-21) | .142 |
| T6 | 16.0 (10-29) | 15.0 (7-21) | .061 |
| *P* | .166 | .782 | |

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; NAG, *N*-acetyl-β-D-glucosaminidase.
[a] Data presented as median (min-max). Significant changes were indicated as bold font.
[b] Mann-Whitney *U* test was used for comparison.
[c] Statistical significance was determined by nonparametric Friedman test for repeated tests at T0 and T6 assay points to examine the precontrast and post-contrast changes. The Wilcoxon signed-rank test was used.

The correlations between contrast volume and changes in SCr values were analyzed by Spearman rank-order correlation.

All statistical analyses were performed using SPSS for Windows version 15.0 (SPSS Inc, Chicago, Illinois).

## Results

Totally, 38 patients (26 male, 12 female) 20 years of age or older who were referred for a clinically indicated coronary angiography were included; 50% received iopamidol (group 1) and the remaining received iodixanol (group 2). We found no significant differences in age, gender, BMI, underlying disease, contrast medium volumes, left ventricular ejection fraction, and demographic factors between the 2 groups (Table 1).

Plasma endothelin, urine NAG/creatinine, and SCr were higher; accordingly, the urine creatinine values were lower in both the groups comparing the 6 hours concentrations to the baseline concentrations (Table 2).

The relationships between the volume of contrast medium and the changes in SCr from baseline to 6 hours after coronary angiography for group 1 and group 2 were all insignificant ($r = .311$; $P = .194$, $r = .236$; $P = .331$, respectively). Relation between endothelin and volume of contrast medium for groups 1 and 2 ($r = -.082$; $P = .748$, $r = -.337$; $P = .158$, respectively), urine NAG/creatinine − volume of contrast medium

($r = -.108$; $P = .661$, $r = -.235$; $P = .334$, respectively), and urine creatinine− volume of contrast medium ($r = .173$; $P = .479$; $r = .069$; $P = .794$), was also nonsignificant.

No differences were found by comparing the 2 groups before the procedure and at 6 hours after the procedure for plasma endothelin, urine NAG/creatinine, serum and urine creatinine, and serum BUN concentrations (Table 2).

## Discussion

Comparing the renal safety of low-osmolar versus isoosmolar contrast agent in low-risk patients, we found similar significant differences in renal function biomarkers such as endothelin, urine NAG/creatinine, and urine creatinine in a short time period after coronary angiography.

In both the groups, none of the patients were diagnosed with CIN with postangiography and at 1-year follow-up. Only 1 patient from group 2 had renal insufficiency, who required hemodialysis 8 months later, whose SCr concentrations were in normal range up to that time. Because CIN is defined as a sudden deterioration in renal function following recent intravascular contrast agent administration in the absence of another nephrotoxic event, it may be diagnosed as a renal adverse effect due to an unidentified reason.[15,16]

The exact pathophysiology of CIN is not well understood. In the etiology, hemodynamic changes (vasoconstriction) and release in endogenous vasoconstrictors such as endothelin and direct tubular injury are suggested.[17] The NAG, which is found mainly in proximal tubular cells, defined in the studies that urinary values are increased earlier than SCr.[9,18,19] Therefore, endothelin and NAG have been reported to be more specific and sensitive to acute changes in kidney function.[18,20] In this study, early changes in these analytes were significant and more sensitive than SCr and BUN. Similarly, in a study by Shaker et al, neutrophil gelatinase-associated lipocalin and cystatin C were more sensitive to acute renal changes than SCr in low-risk patients.[21]

It is suggested that the nephrotoxic effect of iodinated contrast media is proportional to the dose and agent type.[22,23] Several studies compared the renal safety of isoosmolar versus low-osmolar contrast media at high doses with SCr especially in patients with chronic kidney disease.[11,24,25] Feldkamp et al assessed a high volume (>500 mL) in low-risk patients and found no significant difference between the 2 contrast media using urine NAG and creatinine concentrations.[19] In a meta-analysis, iodixanol was found not to be different from nonionic low-osmolar contrast media.[1] The endothelin concentrations increased in plasma and urine in patients who received large volume of contrast agents ($\geq$150 mL) or in patients with renal insufficiency.[26] In this study, we iodinated patients with stable and low baseline SCr ($\leq$1.40 mg/dL) with low volumes ($\leq$62 mL).

In the pathophysiology of CIN, DM is an important risk factor and it is recommended to closely follow-up these patients after preventive therapies with saline hydration with or without forced diuresis, NAC, and statin administration.[16] Due to their antioxidant activity, statins are reported to be useful in the protection against CIN especially in high-risk patients, as oxidative stress is involved in pathogenesis of CIN.[27] In the present study, all the diabetic patients received saline hydration combined with NAC. However, in some studies, saline hydration with or without NAC produced nonsignificant effects on the prevalence of CIN or hydration with sodium bicarbonate provided better protection against CIN.[28,29]

Limitations of this study is that the low number of patients and normal baseline creatinine values reduced the power to detect significant differences between the 2 contrast agents, because the rate of CIN is low (2.5%) in patients with baseline SCr values between 1.2 and 1.9 mg/dL.[7] Another limitation is the that we did not evaluate the dose-dependent nephrotoxic effect of the iodinated contrast medium.[22,23]

We suggest that both contrast agents may be safely used at a low volume for coronary angiography procedure in low-risk patients. Plasma endothelin, urine creatinine, and NAG excretion are more sensitive than SCr and BUN to the acute renal effects of contrast media. We conclude that there is a need for further prospective investigations with more patients and/or with chronic renal disease compared to normal control groups to assess the validity of biomarkers early after contrast medium administration.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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