A Comparison of Nephrotoxicity of Contrast Medium in Elderly Patients who Underwent Renal or Peripheral Arterial Vascular Intervention


Abstract

Objective To compare the nephrotoxicity of iodixanol in elderly patients who underwent a renal artery intervention (RAI) with those who underwent an other peripheral vascular intervention (OPI).

Methods Three hundred fifty-four consecutive patients (>60 years old) received iodixanol during RAI (n=150) or OPI (n=204). The level of serum creatinine (SCr) was measured at the baseline, 24 hours, 48 hours, 72 hours and 1 month after intervention.

Results Within 72 hours after the intervention, the adjusted mean of the peak SCr increase was 11.22 μmol/L [95% confidence interval (CI): 9.21-13.24] in the RAI group and 12.40 μmol/L (95%CI: 10.7-14.09) in the OPI group. The difference in the peak SCr increase was -1.17 μmol/L (95%CI: -3.94-1.60; p=0.406). Contrast-induced nephropathy occurred in 26 patients (17.3%) of the RAI group and in 27 patients (13.2%) of the OPI group (p=0.286). Patients who underwent an RAI showed no increased risk for contrast-induced nephropathy in comparison with patients who underwent an OPI [adjusted odds ratio (OR)=1.108; 95%CI: 0.540-2.273; p=0.780].

Conclusion The nephrotoxic effect of iodixanol in elderly patients who underwent RAI or OPI was comparable.

Key words: iodixanol, nephrotoxicity, contrast-induced nephropathy, peripheral arterial revascularization


Introduction

Although contrast medium (CM) nephrotoxicity is often neglected in clinical practice, contrast-induced nephropathy (CIN) has been reported to range between 11% and 50% in patients with multiple risk factors (1-7). CIN is reported to be the third leading cause of hospital-acquired acute renal failure, which results in increased patient morbidity and mortality (1). Patients with atherosclerotic peripheral vascular disease are often elderly. Concomitant diabetes mellitus, renal impairment, congestive heart failure and hypertension (8-10) increase the susceptibility to the adverse effects of CM (1-7).

Severe hypertension, renal insufficiency or cardiac disturbance caused by renal artery stenosis is often a clinical indication for renal artery intervention (RAI) (11). It is generally thought that renal micro-embolization (the direct injection of CM into the renal artery and repeated transient blockage of the blood flow during the renal revascularization procedures) may sensitize patients to the toxic effects of CM (12). However, it has been unclear whether the incidence of CM-induced renal damage is greater in patients undergoing a RAI.

The purpose of this prospective cohort study was thus to compare the nephrotoxic effect of iodixanol in elderly patients underwent RAI or an other peripheral vascular intervention (OPI).
Materials and Methods

Study participants

The study was conducted at Fuwai Hospital, Beijing, China between December 2011 and February 2014. Patients with peripheral artery diseases, which met the 2011 ESC guideline recommendations for peripheral intervention therapy (13), were eligible for inclusion in the study. All patients were over the age of 60 years and had an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m² [eGFR, mL/min/1.73 m² =186.3 * serum creatinine (Scr, in mg/dL)\(^{-1.154}\) * age\(^{-0.203}\) * 0.742 (if female)] (14). In the RAI group the following three inclusion criteria were applied: (a) the presence of renal artery stenosis of ≥75% via a visual estimate of angiography (or a translesional pressure gradient of ≥20 mmHg peak systolic if renal artery stenosis was ≥60% but <75%); (b) the presence of hypertension that was not controlled by a three-drug therapy (including diuretics), or a systolic blood pressure of ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg when not taking antihypertensive drugs; (c) an ipsilateral renal length of ≥7.0 cm. The exclusion criteria were as follows: patients who received CM within 7 days before study entry, patients who underwent emergent angioplasty, the presence of acute renal failure, a history of hypersensitivity to CM, the presence of congestive heart failure, and patients who were treated with diuretics via parenteral administration. Patients who received N-acetylcysteine, metformin or nonsteroidal anti-inflammatory drugs in the period of 48 hours prior to the procedure (20). Volume expansion with the intravenous administration of isotonic saline solution (2 mL/kg/hour) was initiated 6 hours before the procedure and continued for 24 hours in all patients to reduce the risk of CIN. All patients underwent upper aortic arch and abdominal aorta digital subtraction angiography and lower extremity artery selective angiography (approximately 80-100 mL of CM) to identify the target lesions in the same sitting as the intervention and then catheter-based revascularization procedures were performed. The carotid, subclavian, lower extremity and vertebral stent placements were performed according to the methods of Dong et al. (15), Choky et al. (16), Schillinger et al. (17), and Karameshev et al. (18), respectively. The renal artery stenting procedures were usually performed using the femoral approach (19). A 6F guiding catheter (March1, Boston Scientific, Natikeshi, USA) was used. A 0.014-inch tip-curved guidewire was advanced through the lesions. Predilation of the lesion was usually performed with a coronary angioplasty balloon (4.0×20 mm), and then balloon-expandable bare metal stents (Hippocampus renal RX stent Systems, Medtronic, Minneapolis, USA) were deployed in the lesions. No distal protection devices were used.

Laboratory tests

Blood samples for the SCr measurement were collected at the baseline (on the day before the peripheral intervention and prior to the start of pre-hydration), and at 24 hours, 48 hours, 72 hours and one month after the procedure. The SCr was determined using a UniCel DxC 800 SYNCHRON System (Beckman Coulter, Brea, USA), and the concentration was measured by the Jaffe method. The maximum SCr within 72 hours after the procedure was used to calculate the peak changes in SCr and eGFR. All SCr levels were determined in a blinded fashion by laboratory personnel who measured the levels using an auto analyzer.

Follow-up

The follow-up period was 30 days after the procedure. All of the patients were invited to present themselves to our institute for SCr measurement and other blood tests. During the follow-up examination they were questioned about the occurrence of adverse events, including (but not limited to) myocardial infarction, stroke, bleeding, and dialysis. All of the complications that resulted in an additional procedure, unplanned treatment, prolonged hospitalization, major bleeding (a hemorrhage requiring transfusion or associated with a decrease in hemoglobin ≥2 g/dL), dialysis or death were classified as major clinical adverse events. All complications that caused morbidity or patient discomfort but which did not fulfill criteria for a major clinical adverse event were classified as minor clinical adverse events.

The definition of contrast-induced nephropathy

In the present study, CIN was defined as a relative increase in SCr from the baseline of ≥25% or an absolute increase of ≥44.2 μmol/L (0.5 mg/dL) within 72 hours after the procedure (20).
Table 1. A Comparison of the Demographic and Baseline Characteristics between the RAI and OPI Groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>RAI group n=150</th>
<th>OPI group n=204</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75</td>
<td>25 (16.7)</td>
<td>38 (18.6)</td>
<td>0.634</td>
</tr>
<tr>
<td>Male gender</td>
<td>100 (66.7)</td>
<td>149 (73)</td>
<td>0.195</td>
</tr>
<tr>
<td>Current smoking</td>
<td>63 (42.0)</td>
<td>75 (36.8)</td>
<td>0.318</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40 (26.7)</td>
<td>67 (32.8)</td>
<td>0.211</td>
</tr>
<tr>
<td>Hypertension</td>
<td>150 (100)</td>
<td>148 (72.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>93 (62)</td>
<td>132 (64.7)</td>
<td>0.601</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>61 (40.7)</td>
<td>95 (46.8)</td>
<td>0.252</td>
</tr>
<tr>
<td>Weight, mean ± SD, kg</td>
<td>67.4 ± 11.4</td>
<td>69.3 ± 10.8</td>
<td>0.118</td>
</tr>
<tr>
<td>Body mass index, mean ± SD, kg/m²</td>
<td>24.90 ± 3.04</td>
<td>24.86 ± 3.39</td>
<td>0.927</td>
</tr>
<tr>
<td>SBP, mean ± SD, mmHg</td>
<td>148.21 ± 25.86</td>
<td>132.7 ± 23.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mean ± SD, mmHg</td>
<td>78.78 ± 11.97</td>
<td>75.01 ± 11.83</td>
<td>0.003</td>
</tr>
<tr>
<td>Ejection fraction, mean ± SD, %</td>
<td>63.69 ± 7.07</td>
<td>63.17 ± 6.13</td>
<td>0.455</td>
</tr>
<tr>
<td>Fasting glucose, mean ± SD, mmol/L</td>
<td>5.73 ± 1.70</td>
<td>5.83 ± 1.57</td>
<td>0.557</td>
</tr>
<tr>
<td>Total cholesterol, mean ± SD, mmol/L</td>
<td>4.24 ± 1.20</td>
<td>4.15 ± 0.98</td>
<td>0.431</td>
</tr>
<tr>
<td>HDL, mean ± SD, mmol/L</td>
<td>1.18 ± 0.56</td>
<td>1.19 ± 0.52</td>
<td>0.807</td>
</tr>
<tr>
<td>LDL, mean ± SD, mmol/L</td>
<td>2.49 ± 0.98</td>
<td>2.45 ± 0.81</td>
<td>0.657</td>
</tr>
<tr>
<td>BSC, mean ± SD, umol/L</td>
<td>89.08 ± 27.87</td>
<td>83.94 ± 20.87</td>
<td>0.048</td>
</tr>
<tr>
<td>Baseline eGFR &lt;60 mL/min/1.73 m²</td>
<td>39 (26.0)</td>
<td>28 (13.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Contrast medium volume, mean ± SD, mL</td>
<td>135.1 ± 46.3</td>
<td>138.7 ± 43.4</td>
<td>0.421</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, BSC: baseline serum creatinine, eGFR: estimated glomerular filtration rate

**Statistical methods**

The sample size was calculated for 80% power and a one-sided significance level of 0.025 to declare the non-inferiority of RAI to OPI in terms of the peak change in SCr within 72 hours after the procedure. It was assumed that the peak change in SCr within 72 hours after the procedure was 17.7±26.5 μmol/L (0.2±0.3 mg/dL) in the OPI group. The non-inferiority margin was set at 8.8 μmol/L (0.1 mg/dL). Allowing for a dropout rate of 5%, it was calculated that 300 patients (150 patients per group) would need to be enrolled.

Continuous variables were presented as the mean ± standard deviation, and categorical variables were presented as frequencies and percentages. Categorical variables were compared between the groups by chi-square test or Fisher’s exact test. Continuous variables were compared between the two groups by Student’s t-test or the Mann-Whitney U test. Measurements made in the same patients under two different conditions were compared by paired t-test. The peak change in the SCr and eGFR within 72 hours after the procedure, the SCr increase and the eGFR decrease at 30 days after the procedure were assessed by an analysis of covariance (ANCOVA), with the treatment groups (RAI or OPI) as covariates, and the 95% confidence intervals (CIs) for contrast treatments (RAI minus OPI) were calculated.

Univariate and multivariate logistic regression analyses were applied to assess the independent predictors of CIN and to adjust for confounding factors. The variables identified by the univariate analysis as significant predictors of CIN with p<0.1 and those identified as independent predictors in previous reports were included in the multivariate model. A p value of <0.05 was considered to be statistically significant. All reported p values are two-sided. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS, Chicago, USA).

**Results**

The demographic and baseline characteristics of the 354 patients are listed in Table 1. In the RAI group, the baseline SCr, systolic blood pressure and diastolic blood pressure were higher, and basal eGFR <60 mL/min/1.73 m² and hypertension were more frequent than in the OPI group. The volume of CM administered in the two groups was not significantly different. The remaining demographic and other baseline characteristics between the two groups were similar.

In the RAI group, 150 patients underwent renal stenting, some of whom underwent the simultaneous percutaneous peripheral intervention of other arteries, including 7 (4.7%) carotid arteries, 4 (2.7%) subclavian arteries, 9 (6.0%) lower extremity arteries and 1 (0.7%) vertebral artery. Of the 204 patients in the OPI group, 53 (26.0%) underwent carotid stenting, 62 (30.4%) underwent subclavian stenting, 92 (45.1%) underwent lower extremity artery stenting, and 15 (7.4%) underwent vertebral artery stenting.

Within 72 hours after intervention, the adjusted mean of the peak SCr increase was 11.22 umol/L (95%CI: 9.21, 13.24) in the RAI group and 12.40 umol/L (95%CI: 10.7, 14.09) in the OPI group. The difference in the peak SCr increase was -1.17 umol/L (95%CI: -3.94, 1.60; p=0.406). The upper margin of the 95%CI was below the predetermined non-inferiority margin (8.8 μmol/L), indicating the non-
inferiority of the RAI method in comparison to the OPI method (in terms of the peak change in SCr). The adjusted mean of the peak decrease in the eGFR was 10.94 mL/min/1.73 m² (95%CI: 9.41, 12.43) in the RAI group and 10.31 mL/min/1.73 m² (95%CI: 9.02, 11.61) in the OPI group. The difference in the peak eGFR decrease was 0.63 mL/min/1.73 m² (95%CI: -1.48, 2.74; p=0.560). The dynamic changes of the SCr and eGFR values are shown in Figs. 1 and 2, respectively.

CIN occurred in 26 patients (17.3%) of the RAI group and in 27 patients (13.2%) of the OPI group (p=0.286) within 72 hours after the procedure. There was no significant difference in the increase of SCr value in subjects with CIN between the RAI and OPI groups. An absolute increase of ≥44.2 μmol/L (0.5 mg/dL) in SCr was observed in 5 (3.3%) patients of the RAI group, and 8 (3.9%) patients of the OPI group (p=0.771) (Fig. 4). As shown in Table 2, age ≥75 years, basal eGFR <60 mL/min/1.73 m² and contrast medium volume were determined to be independent predictors of CIN by a multivariate logistic regression analysis. The ejection fraction was significantly negatively correlated with the incidence of CIN. The patients who underwent a RAI did not have an increased risk for CIN in comparison with patients who underwent an OPI (OR=1.108,
1.73 m

while the eGFR decreased from 80.81±21.81 mL/min/1.73 m² to 88.76±26 μmol/L (p<0.001), the eGFR decreased from 80.81±21.81 mL/min/1.73 m² at the baseline to 78.19±20.94 mL/min/1.73 m² at the baseline to 88.76±26 μmol/L (p<0.001), which was significant. In the overall population, the SCr increased from 86.08±24.22 μmol/L at the baseline to 88.76±26 μmol/L (p=0.001), while the eGFR decreased from 80.81±21.81 mL/min/1.73 m² at the baseline to 78.19±20.94 mL/min/1.73 m² (p<0.001) at 30 days after the procedure. The differences between the two groups in the SCr increase (-2.48 μmol/L; 95% CI: -4.92, 0.01; p=0.054) and eGFR decrease (0.33 mL/min/1.73 m²; 95% CI: -2, 2.65; p=0.782) based on the adjusted means from the ANCOVA was not significant. At 30 days after the procedure, a relative increase of ≥25% or an absolute increase of ≥44.2 μmol/L (0.5 mg/dL) in SCr still existed in 15 (4.2%) patients (in the RAI group, n=6; in the OPI group, n=9; p=0.849; Fig. 4). No patients required dialysis.

A minor stroke occurred in one patient in the OPI group one week after the procedure. The patient recovered two weeks later. This was classified as a major clinical adverse event. No other major clinical adverse events occurred in the two groups within the 1 month follow-up period after the procedure. The rate of minor clinical adverse events was similar between the two groups.

### Discussion

To our knowledge, this is the first prospective study to compare the nephrotoxicity of iodixanol between patients who underwent RAI or OPI. The performance of RAI or OPI did not seem to make a difference in term of the peak responses of SCr and eGFR within 72 hours after the intervention. The non-inferiority of RAI to OPI in terms of the peak increase in SCr within 72 hours after intervention was demonstrated. The higher baseline levels of SCr and eGFR (<60 mL/min/1.73 m²) that were seen in the RAI group were possibly caused by severe renal artery stenosis. In spite of these differences, there was no significant difference in the incidence of CIN between the two groups of the present study. After adjustment for potential confounding factors, including the baseline eGFR, the results of the multivariate logistic regression analysis showed that RAI was not a risk factor of CIN (in comparison with OPI). The present study showed that the nephrotoxic effects of iodixanol after RAI were similar to the effects seen after an OPI. The conventional thinking has been that renal micro-embolization caused by renal revascularization procedures may negatively affect renal function and sensitize patients to the nephrotoxic effects of CM. Though this study did not distinguish between the alterations of renal function caused by CM or by renal micro-embolization, the similar nephrotoxic effect that was observed in elderly patients who underwent RAI or OPI indicated that the nephrotoxicity of iodixanol in the RAI group was no greater or even less than that in the OPI group. The present findings are in line with a report by Sabeti et al., which showed no significant difference in the incidence of the deterioration of renal function after renal arteriography and after renal artery angioplasty [8 (15%) vs. 5 (16%); p=1] (21). It is possible that the micro-embolization of plaque-break-ups may not have occurred or may have played only a minor role in the susceptibility to the nephrotoxicity of CM in the RAI group. In addition, renal stenting may have improved the renal perfusion in the otherwise ischemic kidney. This mechanism is supported by Marraccini et al., who reported that the SCr after intervention tended to decrease in patients who underwent renal angioplasty, but increased significantly in patients who underwent percutaneous coronary intervention (22).

In the present study, no patients required dialysis within 30 days after the procedure. Only 15 patients (4.2%) had a relative increase of ≥25% or an absolute increase of ≥44.2 μmol/L (0.5 mg/dL) in SCr at 30 days after the procedure. This suggests that the application of iodixanol was safe in the study population. This is consistent with previous reports indicating that iodixanol has a good safety profile, which is similar or superior to low-osmolar CM (23, 24) and superior to high-osmolar CM (25).

Several limitations were associated with the present study. First, as this is a cohort of patients from a single medical...
center, additional studies will be needed to confirm the results. Second, only one type of CM was used in the study, so we could not compare the nephrotoxicity of iodixanol with the other types of CM. However, given the limited sample size, the use of a single type of CM was conducive to comparing the incidence of CIN among different peripheral territory interventions. Third, a blinded analysis was not performed in the study, which might have led to bias. However, the main indicator of this study, the SCR, was measured by an auto analyzer and was objective. Fourth, the patients with eGFR <45 mL/min/1.73 m² are reported to be at greater risk for CIN (26, 27). In the present study the proportion of patients with eGFR <45 mL/min/1.73 m² was small. The lack of data from the patients with eGFR <45 mL/min/1.73 m² limited the examination of whether the effects of iodixanol in such patients who underwent either RAI or OPI were comparable.

In summary, the present study demonstrated that the nephrotoxic effect of iodixanol in elderly patients who had undergone RAI or OPI was comparable.

The authors state that they have no Conflict of Interest (COI).

References


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