Comparison between gadolinium and iodine contrast for percutaneous intervention in atherosclerotic renal artery stenosis: clinical outcomes

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Abstract

Background. Percutaneous angiography with iodinated contrast in patients with chronic kidney disease carries a risk of contrast nephropathy, which is independently associated with renal disease progression and increased mortality. Gadolinium contrast is a potential alternative to iodinated contrast for percutaneous transluminal renal angioplasty (PTRA), and appears to be safe and well tolerated. The aim of this study was to assess the results of gadolinium use to facilitate PTRA in patients with chronic kidney disease. Methods. Clinical outcomes were compared between patients with serum creatinine (Cr) ≥ 176 µmol/L (2 mg/dL), who had either gadolinium (n = 57; gadoteridol or gadodiamide), iodinated (n = 68; iohexol or ioxidanol) or a combination of gadolinium and iodinated-contrast-enhanced (n = 38) PTRA. Results. Despite similar degrees of pre-procedural renal insufficiency, the incidence of immediate contrast nephropathy [defined as an increase in serum Cr of 44 µmol/L (0.5 mg/dL) within 7 days without other identifiable causes] was lowest in the gadolinium group (3/57, 5.3%) compared to those receiving a combination of modest iodinated contrast in addition to gadolinium (4/38, 10.5%) or solely iodinated contrast (14/68, 20.6%). This was associated with a reduction in the 30-day progression to need for renal replacement therapy (RRT) (P < 0.005). Yet, over a mean follow-up of 40 ± 22 months, renal function outcomes or all-cause mortality were not different between the contrast groups. The type of contrast used had no effect on technical success and both short- and long-term blood pressure outcomes were comparable between the groups. Two patients developed pathology-proven nephrogenic fibrosing dermopathy, a serious skin condition that has been seen in patients with kidney disease following administration of gadolinium.

Conclusions. Gadolinium contrast appears to be an effective agent for interventional renal angiograms. Compared to iodinated contrast, gadolinium contrast is associated with a significantly lower incidence of contrast nephropathy and early progression to end-stage renal disease (ESRD) in patients with pre-existing chronic kidney disease. The risk of fibrosing dermopathy however and remains to be established.

Keywords: atherosclerotic renal artery stenosis; contrast media; contrast nephropathy; gadolinium angiography; ischaemic nephropathy; percutaneous transluminal angioplasty

Introduction

The introduction of endovascular procedures has expanded the therapeutic options for patients with atherosclerotic renal artery disease, who are frequently poor surgical candidates due to multiple comorbidities and advanced age [1]. In current practice, percutaneous transluminal renal angioplasty (PTRA) coupled with renal artery stenting is first line therapy for preservation of renal function and treatment of renovascular hypertension resistant to medical therapy in these patients [2]. However, the use of iodinated contrast during endovascular procedures carries a risk of toxicity, especially for a subset of patients with pre-existing chronic kidney disease who are at a particularly high-risk for developing contrast nephropathy [3,4]. In fact, nephropathy that develops after coronary angiography has been associated with permanent impairment of renal function, increased in-hospital and long-term mortality [5,6].

One approach to decrease the risk of contrast nephropathy is to develop effective preventive measures. Extensive research to date has failed to identify a preventive strategy that consistently adds to the modest benefit seen with hydration [7–11]. Another approach is to use an alternative, less nephrotoxic contrast agent. Results from several case
series and isolated case reports support a role for gadolinium agents for angiography of renal [12–16] and other vascular beds [17–22] and suggest improved renal safety in patients with chronic kidney disease. A major limitation of these studies is the lack of an appropriate control group that, ideally, should consist of patients with a similar degree of renal insufficiency who have undergone renal angiography with iodinated contrast. Another concern for the use of gadolinium in place of iodinated contrast is its inferior image quality, which may have a negative impact on visualization and thus on the technical success of endovascular procedures. To date, published studies provide limited data regarding the use of gadolinium for interventional renal angiograms and long-term outcomes with respect to blood pressure control and renal function.

The objective of this study was to compare the safety and technical success between gadolinium and iodine-enhanced renal angiography by studying the short- and long-term outcomes of 163 patients with significant pre-existing azotemia [serum creatinine (Cr) ≥ 176 µmol/L (2 mg/dL)] who received one or both of these contrast agents for intra-arterial digital subtraction angiography, coupled with PTRA, at our institution between January 1998 and July 2005.

Subjects and methods

Subjects

Eligible subjects were those patients with significant renal impairment [defined as a pre-procedure serum Cr ≥ 176 µmol/L (2 mg/dL)] that underwent PTRA between January 1998 and July 2005. All patients had PTRA for ACC/AHA Class IIa indications of either accelerated or medically resistant hypertension or presumed ischaemic nephropathy (progressive renal disease in the setting of significant bilateral renal artery stenosis or stenosis to a solitary kidney) [23]. This study period was chosen to identify comparable cohorts of patients who had either gadolinium contrast or conventional iodinated contrast and to allow sufficient time for follow-up. The protocol was approved by the Institutional Review Board and all subjects consented to the use of their records for research.

Relevant clinical data (Table 1) were abstracted from each of the patients’ records, which included documentation of outpatient, inpatient and emergency room visits at the Rochester Mayo Clinic, as well as correspondence from other medical providers. If patients had more than one percutaneous revascularization procedure, data were abstracted from the first procedure only. Patients were excluded if they had no serum Cr measurement within 1 week of angiography or had received contrast either in the preceding 14 days or further contrast within 2 weeks of angiography. All patients fulfilled the definition of National Kidney Foundation stages 3–5 chronic, non-dialysis-dependent kidney disease [24].

Comparative analysis

The group receiving gadolinium contrast (n = 57) was compared to the group of patients who underwent renal artery revascularization over the same study period, but who received solely conventional iodinated contrast (n = 68). The third group of patients received a combination of both gadolinium-based and iodinated contrast for angiography (n = 38).

Interventional technique

Intra-arterial digital subtraction angiography was performed using standard techniques. Arterial access was obtained with 5F or 6F intra-arterial sheaths by using the modified Seldinger technique, with the right femoral artery as the preferred access site. Renal artery angioplasty was performed after aortography and selective renal angiography. Angioplasty was typically performed for stenoses exceeding 70% of the diameter or for a pressure gradient of at least 10 mmHg across the stenotic lesion. The decision to proceed with adjuvant stent placement (142/163) was made at the discretion of the operator. All patients underwent heparin infusion to achieve an activated clotting time of at least 200 s during stent placement. Technical success was defined as a post-interventional residual stenosis <20%.

Clinical factors

Average blood pressure values obtained during outpatient visits were used for this analysis. Hypertension was defined

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<th>Table 1. Baseline characteristics</th>
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<tr>
<td>Gadolinium</td>
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<tr>
<td>---------------------------------</td>
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<tr>
<td>Age (years), mean ± SD</td>
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<tr>
<td>Weight (kg), mean ± SD</td>
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<tr>
<td>Body mass index, mean ± SD (kg/m²)</td>
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<td>Sex (male), number (%)</td>
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<td>Medical history, number (%)</td>
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*P < 0.02 between the gadolinium group and the iodinated group.
as the presence of a persistent systolic blood pressure > 140 mmHg, a diastolic blood pressure > 90 mmHg or the use of medication for the treatment of elevated blood pressure [25]. Mean arterial pressure was calculated as (systolic + twice diastolic pressure)/3. Body mass index was defined as pre-procedural body weight (kg) divided by the square of the height (m). Serum Cr levels were available both before and within the first 7 days after renal angioplasty for all patients. Cr clearance was estimated by the equations of Cockcroft–Gault [26]. The primary endpoint was the development of contrast nephropathy that was defined as post-procedural increase in serum Cr of 44 µmol/L (0.5 mg/dL) within 7 days after the intervention without other identifiable causes of worsening in renal function. Long-term follow-up of blood pressure and renal function outcomes were ascertained as of the last available clinic visit. Mortality status was available from the records in 137 cases; for the remaining 26 cases, it was determined from the social security death index.

Statistical analysis
Statistical analyses were performed using JMP version 6.0 (SAS Institute Inc., NC, USA) and are presented as mean ± standard deviation or median with interquartile range, if skewed. The mean difference between groups is expressed with 95% confidence intervals. Statistical procedures included simple correlation analysis, analysis of variance, paired t-test, chi-square analyses, Kaplan–Meier survival analysis, proportional hazards and bivariate fitting with simple linear regression. A P < 0.05 was predetermined.

Results
Baseline characteristics
Of 848 PTRA procedures performed at our institution between January 1998 and July 2005, 163 patients (19%) had significant pre-existing azotemia [serum Cr ≥ 176 µmol/L (2 mg/dL)] not on dialysis and had baseline and follow-up Cr levels available. The majority of patients had stage 4 chronic kidney disease (132, 81%) with 25 (15%) having stage 3 and 6 (4%) having non-dialysis-dependent stage 5. The primary contrast material used for imaging in these 163 cases was gadolinium alone in 57 and iodinated contrast alone in 68 procedures with a combination of gadolinium and iodinated contrast in 38. Baseline demographic features were similar between the two groups (Table 1) except for modestly worse renal function, lower diastolic blood pressure and a greater mean number of antihypertensive medications in those patients who received gadolinium versus those who received iodinated contrast (Table 1).

Contrast nephropathy strategies
Most patients were administered prophylactic hydration and highest when iodinated contrast was used exclusively (Table 2; P < 0.01). The majority of patients in both groups had adjuvant stenting and there was no difference in the rate of technical success across groups (Table 2).

The type of contrast varied over time, reflecting the changes in practice at our institution. The majority (48%) of patients in the gadolinium group received gadoteridol (Prohance™) and the remainder (52%) gadodiamide (Omniscan™). With respect to the iodinated contrast used, most (58%) received iohexol (Omnipaque™) and the remainder (42%) ioxaglate (Visipaque™). The total volume of contrast administered during the procedure varied and was the lowest for gadolinium used alone, intermediate for gadolinium with supplemental iodinated-contrast administration and highest when iodinated contrast was used exclusively (Table 2; P < 0.01).

Contrast nephropathy
The incidence of contrast nephropathy, defined as a post-procedural increase in serum Cr of 44 µmol/L (0.5 mg/dL) within 7 days after the intervention without other identifiable causes of worsening in renal function, was highest in the iodinated group 14/68 (20.6%) versus the gadolinium contrast group 3/57 (5.3%), P < 0.01 and intermediate in the group of patients receiving a combination of gadolinium and iodinated contrast (Table 1).

Table 2. Peri-procedural characteristics

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Gadolinium</th>
<th>Gadolinium and iodinated</th>
<th>Iodinated</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>57</td>
<td>38</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Contrast nephropathy preventive strategies</td>
<td></td>
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<tr>
<td>Intra-venous fluids</td>
<td>N-acetyl-cysteine</td>
<td></td>
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<tr>
<td>Gadolinium-based contrast</td>
<td>76 ± 40</td>
<td>55 ± 35</td>
<td>–</td>
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<tr>
<td>Iodinated contrast</td>
<td>–</td>
<td>37 ± 37</td>
<td>102 ± 50</td>
<td>0.01</td>
</tr>
<tr>
<td>Cumulative contrast volume</td>
<td>76 ± 40</td>
<td>92 ± 42</td>
<td>102 ± 50</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjuvant stenting</td>
<td>51 (89%)</td>
<td>32 (84%)</td>
<td>59 (87%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Rate of immediate technical success</td>
<td>52 (93%)</td>
<td>35 (92%)</td>
<td>64 (94%)</td>
<td>0.7</td>
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and iodinated contrast (4/38; 10.5%). In the gadolinium group, the mean serum Cr decreased within 7 days following renal angioplasty by 9.4 ± 26% (P < 0.01). Within the same time frame, those patients receiving primarily iodinated contrast tended toward an immediate increase in serum Cr by 4.3 ± 33%. To examine whether the opposite Cr trends and differences in the incidence of post-procedure nephropathy between the groups were related to the differences in the proportion of unilateral versus bilateral procedures within the groups, we performed a separate subgroup analysis in patients who had unilateral revascularization in the presence of two functional kidneys. The incidence of post-procedure nephropathy was still higher in the iodine (10/42; 24%) versus the gadolinium group (1/22; 4.6%, P = 0.04) with an intermediate incidence in the gadolinium/iodinated combination group (2/15; 13%). In addition, these subgroup of patients showed the same Cr trends 7 days after the intervention as the total cohorts: patients in the gadolinium group demonstrated an average decrease in serum Cr (−11.5 ± 23%) while those in the iodine group experienced an increase in serum Cr (8 ± 37%; P = 0.02).

The dose of gadolinium-based contrast did not correlate with the rise in Cr or the development of contrast nephropathy. However, for the iodinated-contrast group, the volume of iodinated contrast tended to be greater in those developing immediate post-procedure nephropathy: 121 ± 59 mL of iodinated contrast as compared to 96 ± 47 mL of iodinated contrast in those who did not (P = 0.08). In multivariate analysis using a stepwise inclusion model, the only significant predictors of contrast nephropathy were the volume of iodinated contrast (P = 0.02) and the patients’ age (P = 0.04). We performed a separate subgroup analysis with matched gadolinium- and iodinated-contrast volumes. Here the incidence of contrast nephropathy was 4.6% (2/42) in a group who received a mean gadolinium dose of 72.2 ± 21 mL compared to a rate of 19.1% (8/42) in a group of patients who received a mean iodinated-contrast dose of 71.3 ± 23 mL (P < 0.05).

In further subgroup analysis, the use of N-acetyl-cysteine or the type of iodinated contrast (iohexol versus iodixanol) did not significantly affect the incidence of contrast nephropathy and the time for the measurement of follow-up Cr was similar across groups.

Clinical outcomes

Development of contrast nephropathy was associated with a greater progression to the need for permanent dialysis or transplantation (Figure 1A; P < 0.0001) over a mean follow-up of 40 ± 22 months. The presence of diabetes mellitus did not affect the long-term progression to the need for RRT. Overall long-term survival was poor with a median survival of 58.2 months comparable to mortality rates observed in a large previously published registry of renal artery stents [29]. All-cause mortality was also increased (Figure 1B; P < 0.05), with a 30% 1-year mortality in those patients who developed acute deterioration in renal function versus 12% 1-year mortality in those who did not with the mortality rate in these groups merging over time (Figure 1B).

Over long-term follow-up, the level of blood pressure control was equivalent across groups (gadolinium—144/66 mmHg on 2.7 medications; combined contrast group—145/70 on 2.8 medications and iodinated contrast—140/68 mmHg on 3.1 medications). Those patients who received iodinated contrast had a 7.2% incidence of requiring permanent dialysis or transplantation within 30 days compared to 0% in the gadolinium group (P < 0.005) with an overall significantly increased incidence of dialysis or transplantation at 90 days (Figure 2A). However, over time, this difference declined with no difference across groups over long-term follow-up (Figure 2B; P = 0.5). There was also no difference in mortality across contrast groups (Figure 2C; P = 0.2).

Nephrogenic fibrosing dermopathy

In review of the records of the 95 patients who received a gadolinium-based contrast agent, we identified 2 cases with pathology-proven nephrogenic fibrosing dermopathy. Both cases were men with ages 63 and 67. Subsequent to their index PTRA s in 2003, both eventually became haemodialysis dependent. Gadolinium exposure with PTRA was not exclusive of diagnostic contrast-enhanced MRIs and/or MR angiograms that occurred around the same time.
Gadolinium-based contrast for PTRA

Fig. 2. Patients receiving gadolinium contrast alone had a lower incidence within 3 months of the need for dialysis of transplantation (A; $P = 0.009$) although this difference did not persist over time (B; $P = 0.48$). No association of contrast use with incidence of all-cause mortality (C; $P = 0.2$).

Discussion

Our results demonstrate the safety and efficacy of gadolinium-based renal artery revascularization in patients with pre-existing renal dysfunction in comparison to a similar group of patients receiving iodinated contrast. Both contrast agents allowed satisfactory vascular imaging to induce technical success rates exceeding 92% in all groups, although potentially a proportion of patients in the combined contrast group received supplemental iodinated contrast to aid in angiography. Gadolinium was associated with a substantially lower incidence of deteriorating kidney function (5.3%) as compared to iodinated contrast (20.6%). Those patients who developed contrast nephropathy were at an increased risk for progression to ESRD and an elevated increased early mortality. Consistent with the higher rate of contrast nephropathy in the iodinated-contrast group, their rate of progression to the need for permanent RRT within a month was significantly higher. These results extend previous reports and demonstrate substantial early benefit to endovascular procedures based on gadolinium contrast.

With respect to renal outcomes following PTRA with or without stenting, several studies indicate that clinically significant improvement occurs in 25–30%, no significant change occurs in 45–50% and worsening of renal function occurs in up to 25% of patients [27,28,30,31]. Contrast nephropathy is one of the several possible causes of worsening renal function following percutaneous renal artery revascularization. Others include reperfusion injury and atheroembolic disease. Several strategies for the prevention of contrast nephropathy have been studied with an emphasis on high-risk patients, including those with chronic kidney disease. Pre-procedural hydration techniques have decreased the incidence but have not solved completely the problem of contrast nephropathy [4]. An alternative approach relies on the use of non-ionic, low- or iso-osmolar iodinated contrast or media with fewer nephrotoxic effects. Not surprisingly, several endovascular interventional studies recently and have explored the use of gadolinium (known for its renal safety when administered intravenously) as a contrast agent for peripheral arterial procedures in patients with chronic kidney disease [21,32–34]. In general, these studies suggest that gadolinium is an intra-arterial contrast medium for endovascular interventions.

Few studies address the use of intra-arterial gadolinium as a contrast agent for digital subtraction angiography of the renal vasculature and support its safety and efficacy for both diagnostic and therapeutic purposes [13–15,35]. Most of these studies do not include a comparison group. All but one [15] limit their comparisons regarding the safety of gadolinium to the incidence of renal failure in their patient cohort (2.3–8%) versus the literature-reported incidence of post-procedural nephropathy. A single study that compared the incidence of a post-procedural rise in Cr levels between patients who underwent gadolinium and CO2-enhanced renal angiography to those who underwent renal angiography with iodinated contrast in the same institution, reported only a marginal ($P = .0507$) benefit of gadolinium-based contrast. Results from our study present a more direct comparison of gadolinium to iodinated contrast in a larger patient sample. Our results demonstrated a clear benefit of gadolinium with respect to a lower incidence of contrast nephropathy. Within the iodinated-contrast group, deteriorating renal function after endovascular procedures was associated with a high rate of progression to ESRD and an increased mortality.
It is important to emphasize that patients in the iodinated group on average and received slightly higher amounts of contrast than those who received either gadolinium only or gadolinium with supplemental iodinated-contrast administration. Therefore, the observed difference may be due in part to the lower volume of gadolinium being used rather than a lower nephrotoxic potential compared to iodinated contrast. In a subgroup analysis was performed in which 42 patients receiving gadolinium were matched for contrast volume with 42 patients who received iodinated contrast. The difference in rates of contrast nephropathy between the groups persisted, suggesting that not only the volume, but the type of contrast itself contributes to contrast nephropathy risk. But, why did patients in the gadolinium group receive a lower volume of contrast than those in the iodinated-contrast group?

We believe that the most likely explanation derives from more stringent application of published guidelines concerning dose and volume limitations that were designed for intravenous gadolinium use. In contrast, specific limitations do not exist as to the amount of iodinated contrast to be administered, although numerous studies indicate that the risk of contrast nephropathy is related to the volume of contrast being used. This premise reinforces our results indicating that patients who developed worsening renal function in the iodinated-contrast group received more contrast than those who did not.

Both our data and previous series suggest that a certain proportion of patients who have received gadolinium will still develop transient worsening of renal function without other identifiable causes. Whether this is a function of the volume of gadolinium being used remains to be determined.

Most of our patients received a total amount of gadolinium contrast that did not exceed the recommended dose of 0.3–0.4 mmol/kg or 0.6–0.8 mL/kg. The dose of gadolinium that was administered to the three patients who developed acute renal failure (30, 60 and 62 mL, respectively) did not exceed the mean dose of gadolinium for the group as a whole (76.5 ± 40 mL). In addition, no significant correlation was apparent between the dose of gadolinium contrast and a rise in Cr (P = 0.8), even in those patients who developed an insufficient rise in Cr to meet criteria for contrast nephropathy. Finally, subgroup analysis matched for contrast volume indicated a similar propensity for a higher rate of contrast nephropathy with iodinated versus gadolinium-based contrast. These three observations argue against a direct correlation between the volume of gadolinium contrast and post-procedure nephropathy.

A major limitation to the use of gadolinium for endovascular procedures is its potentially inferior vascular enhancement and image quality compared to iodinated contrast. In principle, lower-quality images will have a negative impact on the quality of intervention. The results of our study indicated that both early technical success and long-term clinical outcomes between the groups were not different, consistent with adequate vascular imaging to achieve successful intervention. Because this group is recognizable at higher risk than many others, it may be argued that additional imaging procedures, e.g. MR angiography and/or Doppler ultrasound, should be considered to delineate the likely sites requiring careful image definition and intervention.

Despite considerable differences in early deterioration of renal function after vascular procedures and early progression to need for RRT, no differences were observed regarding long-term measures. This is likely related to the fact that this cohort of patients have a high prevalence of vascular disease and so any benefit of a decreased incidence of contrast nephropathy may be simply overcome by their inherent high risk for renal and cardiovascular complications and progression of their underlying disease. Details with regard to further contrast exposures (more than a month after index PTRA) were inadequate to assess the impact on long-term renal function. Hence it is likely that further contrast exposures may have contributed to deteriorations in renal function across all groups.

**Conclusion**

Limitations of our study stem from its retrospective design and a consequent absence of a systematic, prospective comparison of clinical outcomes and adverse effects between the groups. However, our results clearly demonstrate that gadolinium is an effective contrast agent for percutaneous renal artery angioplasty when used in currently recommended doses. Gadolinium use was associated with a substantially lower incidence of contrast nephropathy in a large cohort of patients with significant baseline azotemia that translated into a reduction in the need to commence permanent RRT within 1 month. Future prospective randomized studies are required to confirm the cost-effectiveness, renal and overall safety with respect
to both short- and long-term outcomes of intra-arterial gadolinium versus iodinated contrast used for renal endovascular procedures in patients at high risk for contrast nephropathy. Further studies are required before these findings can be extrapolated to other vascular beds.

Conflict of interest statement. None declared.

References


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