Ultra-Low dose contrast using Transluminal Renal Angioplasty (ULTRA study)

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Abstract

Background

Severe atherosclerotic renal artery stenosis (ARAS) is a predictor of future cardiovascular events and should be managed effectively. This study aimed to validate the safety and efficacy of percutaneous transluminal renal angioplasty (PTRA) using low concentration digital subtraction angiography (LC-DSA) among patients with severe ARAS and advanced chronic kidney disease (CKD).

Methods

This prospective study conducted between August 2018 and August 2020. Patients with CKD stage 3b or worse and significant renal artery stenosis were included in this study and underwent PTRA with ultra-low dose contrast medium. The primary endpoint was a change in renal function, based on serum creatinine (sCr) levels.

Results

Thirteen lesions of eleven patients underwent PTRA for ARAS with ultra-low dose contrast medium. Mean sCr level has significantly improved from 3.18 ± 1.8 mg/dL (before procedure) to 2.34 ± 1.17 mg/dL (one month after treatment) ($p = 0.039$). The mean amount of used contrast was 8.8 ± 4.0 ml per vessel. Patients with renal artery stenosis $>80\%$, peak systolic velocity >300 cm/m², or CKD Stage 3b were analyzed. More severe stenosis and rapid deterioration of renal function before treatment were associated with improved kidney function. No cardiovascular and renal complications, such as stroke or contrast-induced nephropathy, were noted in any of the patients.

Conclusions

PTRA with ultra-low dose contrast medium is safe and provides good results.

Trial registration: Investigation for optimal protocol using diluted ionic contrast medium during angiography, UMIN000034174. Registered 26 September 2018,

https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000038955

Background

Severe atherosclerotic renal artery stenosis (ARAS) is a cause for dialysis (1), and a predictor of future cardiovascular events (2). Although there were some small trials that indicated that percutaneous transluminal renal artery angioplasty (PTRA) improved renal function (3–7), randomized controlled trials (RCTs) have shown no difference in renal function or cardiovascular events between guideline-directed medical therapy (GDMT) alone and PTRA with GDMT (8–10). However, unlike the previous result, a recent report demonstrated that PTRA reduced the cardiovascular events in the group with improved renal

function (11). Therefore, it is important to identify who can benefit from PTRAs and provide them with treatment opportunities.

One of the reasons why PTRAs has failed to show effectiveness for renal function in the RCTs is the use of large amount of contrast media up to about 125mL (12), and PTRAs may be useful in select patients depending on the severity of lesions and degree of chronic kidney disease (CKD). Endovascular therapy using diluted contrast has been suggested to prevent contrast-induced nephropathy (CIN); (13) however, the safety and efficacy of PTRAs using diluted and reduced contrast is unknown.

This study aimed to validate the safety and efficacy of PTRAs using low concentration digital subtraction angiography (LC-DSA) among patients with severe ARAS and advanced CKD.

Methods

Study design and population

This study followed a single center, prospective, observational design. The study was approved by the ethics committee of our institution and registered with the University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR), as recommended by the International Committee of Medical Journal Editors (no. UMIN000034174).

This study included consecutive patients who underwent PTRAs with ultra-low dose contrast medium in our institution between August 2018 and August 2020. The eligibility criteria were (1) CKD stage 3b or worse and (2) significant renal artery stenosis, defined as stenosis of at least 80% on computed tomography or magnetic resonance imaging or as peak systolic velocity ≥ 300 cm/sec on renal duplex ultrasonography. The exclusion criteria included renal atrophy defined as < 7 cm kidney size, renal artery stenosis due to fibromuscular dysplasia, previous initiation of dialysis, cholesterol crystal embolization, or PTRAs during endovascular aneurysm repair.

Procedure

The patients were placed on dual antiplatelet therapy with aspirin and thienopyridine before the procedure. A 4.5 French guiding sheath was inserted in a radial or femoral artery and advanced to the renal artery with the non-touch technique. LC-DSA was performed to detect renal artery stenosis (Figure 1A, B). In some cases, a hydro-coated wire was used to cross the lesion. Pre-dilatation was performed, and a stent was deployed in all cases with ostial lesions (Figure 1C). A complete angiogram to assess the entire kidney was also performed (Figure 1D).

The primary endpoint was a change in sCr levels, which was assessed by comparing measurements one month before and after PTRAs. The secondary endpoints were dose of contrast medium, procedure complications, renal events, and major adverse cardiovascular events.

Angiography was performed using the Alphenix INFX-8000H (Canon Medical Systems, Tustin, California, USA). To obtain high quality angiographic images, DSA parameters were adjusted to improve image sensitivity and contrast and reduce edge intensity.

The contrast used in the procedure was diluted in a solution containing 1 mL of Iopamidol 755 mg / mL contrast medium and 9 mL of saline. The contrast medium was the same as that used in standard PTRa. In all cases, saline was administered at 1mL/kg for 12 hours prior to the procedure.

Definition

Procedure complications were defined as vessel rupture, any bleeding requiring blood transfusion, and cholesterol crystal embolization. Renal events were defined as CIN, dependence on hemodialysis, and renal transplantation. Major adverse cardiovascular events were defined as death, myocardial infarction, hospitalization for congestive heart failure, and stroke. The definition and classification of CKD were introduced by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative in 2002. Procedure success was defined as residual stenosis <30% without flow delay. CIN was defined as an elevation of serum creatinine (sCr) of more than 25% or ≥ 0.5 mg/dL (44 μ mol/L) from baseline within 48 h.

Statistical Analysis

All statistical analyses were performed using SPSS (SPSS Inc., Chicago, Illinois, USA). Continuous variables are reported as mean $\pm$ standard deviation (SD), whereas categorical variables were presented as numbers with percentages. Continuous variables were examined using the paired t-test or Mann–Whitney U test. A *P* value <0.05 was considered statistically significant.

Results

Patient characteristics

Fifteen lesions were treated in thirteen patients. Two cases were excluded because they underwent PTRa during endovascular aortic repair for an abdominal aortic aneurysm and aortic dissection, respectively. Overall, 13 lesions of 11 patients, and 12 procedures were examined. The baseline characteristics of our patients are presented in Table 1.

All patients had hypertension and dyslipidemia. The patients were on an average of 2.5 antihypertensive agents (i.e., diuretic, calcium-channel blocker, beta-blocker, renin angiotensin system [RAS] blocker, and alpha-blocker); seven (63.6%) patients were taking RAS blockers at baseline. The mean lesion stenosis was 91%, and two cases demonstrated total occlusion of the involved artery.

Procedure results

The procedural data are shown in Table 2. The mean amount of used contrast was 9.5 ± 3.5 mL per procedure and 8.8 ± 4.0 mL per vessel. None of the cases required an intravascular ultrasound (IVUS) or

distal protection devices.

Primary and secondary outcomes

Figure 2 shows the mean sCr levels before (3.18 ± 1.8 mg/dL) and one month (2.34 ± 1.17 mg/dL) after treatment ($p = 0.039$). A $\geq 20\%$ decrease in sCr was documented in five patients, whereas the sCr level remained unchanged (within $\pm 20\%$ of the pre-treatment value) in six patients. None of the patients demonstrated a $\geq 20\%$ increase in sCr levels compared to pre-treatment values.

The cases were analyzed depending on whether they responded to the intervention. The responder group was comprised of patients who demonstrated an improvement of at least 20% in sCr levels, whereas the non-responder group showed changes within 20% of the corresponding pretreatment values.

Table 3 compares the patients and procedure characteristics between these two groups. Figure 3 shows the time course of sCr levels in these two groups. The responder group tended to have the most recent worsening of renal function. In the responder group, the average extent of renal artery stenosis was 99.4% (range, 99–100%), whereas most of the patients in the non-responder group had less than 90% stenosis. Renal function tended to be worse in the responder group. Age, gender, history of other atherosclerotic disease (coronary artery disease, peripheral artery disease, cardiovascular disease), or proteinuria >1.0 g/gCr did not contribute to the primary outcome. Patients with progressively reduced renal function and renal artery stenosis of at least 99% were more likely to benefit from PTRAs.

No cardiovascular events and complications were noted during our study. While renal function deteriorated slightly in some cases, none of them met the definition of CIN. One patient was temporarily started on hemodialysis but stopped three weeks after PTRAs.

Discussion

This prospective study demonstrated that PTRAs with ultra-low volume contrast was safe and improved renal function.

Previous RCTs failed to show the superiority of PTRAs to GDMT, because PTRAs have been associated with distal embolization, cholesterol embolization and CIN. Some studies demonstrated the benefit of using distal protection systems to improve renal functions (12, 14). However, distal protection systems are difficult to use during PTRAs, because of a short landing zone. These are not generally applied to endovascular procedures with the exception of carotid artery stenting.

CIN is a major complication of catheter interventions. The most effective method to prevent CIN is to reduce the amount of contrast medium; however, it is difficult to reduce the amount of contrast medium in normal angiography (12, 15, 16); the average volume of iodinated contrast medium used in the previous studies was approximately 100 mL. Some studies have proposed that carbon dioxide (CO₂) can be used as a safe and effective contrast medium, however, the recent CO₂ angiography registry reported a mortality rate of 2% (2/100) (18). The routine use of CO₂ is currently not recommended.

Hayakawa et al. demonstrated the efficacy of using diluted contrast for endovascular therapy of the lower extremity (13). By using LC-DSA, they were able to dramatically reduce the amount of required contrast without using IVUS. While an IVUS can reduce the contrast requirement in some cases, it is only useful for precise stent positioning. Moreover, an IVUS cannot evaluate the renal artery ostium or determine whether the angiography has been completed; its use in PTRAs is limited. A major limitation of LC-DSA is motion artifact; abdominal gas oftentimes interrupts the clear renal artery imaging. Abdominal gas should be managed in cases where LC-DSA will be used.

Among patients with ARAS and CKD, the benefits of renal artery revascularization may be limited if the renal dysfunction was due to other causes, such as cholesterol crystal embolization or renal parenchymal disease. In this study, almost all patients were referred to our institution by nephrologists, which meant that patients were evaluated properly and assessed to most likely benefit from revascularization procedures. Simple stenosis screening may be inadequate when considering the need for renal revascularization.

Lesion selection is also an important factor for obtaining good results. The Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial examined a large number of cases with moderate stenosis. Stenosis measurements were performed in different sites instead of a single laboratory, (9) and stenosis rates of 70–80% or more were considered significant to require revascularization (24). However, the ASTRAL trial demonstrated that stenting moderate lesions may not significantly improve renal function. Moreover, the study showed that patients with more severe stenosis, such as those close to obstruction, were more likely to benefit from revascularization. The ASTRAL trial also highlighted the impact of renal function on overall procedural success. The mean estimated glomerular filtration rate in the ASTRAL and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trials ranged from 39.8–58 mL/min/1.73 m². Compared to these trials, the renal functions of our patients were significantly worse at 23.5 mL/min/1.73 m². The difference in the results between the studies may be due to differences in the degree of stenosis and renal function in the study populations.

Previous studies suggested that PTRAs may be more effective in patients with low albuminuria (19, 20, 21) or who present with a rapid decline in renal function (21, 22, 23). This study demonstrated that proteinuria did not contribute to the primary outcome; however, patients who presented with a rapid decline in renal function were more likely to benefit from PTRAs.

This study has some limitations. First, this was a single-center prospective study that examined a small sample of patients. The results have to be validated by a multi-center prospective study that examines a larger sample population. Second, motion artifacts may have significantly decreased the image quality provided by LC-DSA. Subtraction divergence resulted in high degrees of image noise that made it difficult to manage abdominal gas. Third, none of the patients in this study used IVUS or distal protection systems. Lastly, we did not examine patients with fibromuscular dysplasia.

In conclusion, PTRAs with ultra-low dose diluted contrast medium was safe and improved renal function in some cases.

Abbreviations

ARAS

atherosclerotic renal artery stenosis

CIN

contrast induced nephropathy

CKD

chronic kidney disease

CO₂

carbon dioxide

GDMT

guideline-directed medical therapy

IVUS

intravascular ultrasound

LC-DSA

low concentration digital subtraction angiography

POD

postoperative day

PTRA

percutaneous transluminal renal angioplasty

RAS

renin angiotensin system

RCTs

randomized controlled trials

SD

standard deviation

sCr

serum creatinine

Declarations

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Authors' contributions

MK and KS performed the literature review and drafted the manuscript. TT was the consultant who participated in the study design and edited the manuscript. KS, AE, NF, and HH were the interventionists who performed PTRAs in the cases. AK, KF, MK and MR were the nephrologists who evaluated patients renal functions and assisted in data collection. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

Approval by the ethic committee of Tokyo Saiseikai Central Hospital.

Consent for publication

Not applicable.

Competing interests

NF receives consulting fee from Cook Medical, Endologix, Medtronic, and WL. Gore. KS receives honorarium from Boston Scientific. NF receives honorarium from BD, Boston Scientific, Canon, Cook Medical, Cordis, Medtronic, Terumo, and WL. Gore. KS receives payment for expert testimony.

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Tables

Table1. Baseline characteristics of this study population (n=11).

Age (years)	73.5 ± 11.6
Male sex (n)	8 (73%)
BMI (kg/m ²)	24.0 ± 3.4
Smoking history (n)	7 (64%)
Hypertension (n)	11 (100%)
Dyslipidemia (n)	11 (100%)
Diabetes mellitus (n)	4 (36%)
Number of antihypertensive drug type (n)	2.5 ± 0.9
RAS blockers therapy (n)	7 (64%)
Statin (n)	9 (82%)
Antiplatelet (n)	10 (91%)
Previous cardiovascular disease (n)	5 (46%)
Previous peripheral arterial disease (n)	3 (27%)
Previous cerebrovascular disease (n)	2 (18%)
Serum creatinine level (mg/dL)	3.18 ± 1.78
Estimated GFR (mL/min/1.73m ²)	23.5 ± 17.2
Urinal protein/Creatinine (g/gCr) *	0.68 ± 0.77
Bilateral lesion (n)	2 (18%)
Degree of stenosis of the most affected kidney (%)	91.0 ± 10.4

Data are numbers (n) (%) or mean values ± standard deviation (SD).

BMI = body mass index, RAS = renin angiotensin system, GFR = glomerular filtration rate

*n=10. One of the eleven did not measure urinary protein.

Table2. Procedure data (n=12).

Lesion length (mm)		9.8 ± 2.0
Reference diameter (mm)		4.8 ± 0.7
Approach site (n)	Trans-radial	8 (667%)
	Trans-femoral	4 (33%)
Stent diameter (mm)		5.2 ± 0.8
Stent length (mm)		17.9 ± 1.7
Use of Intravascular ultrasound (IVUS)		0 (0%)
Dose of contrast (mL)		9.5 ± 3.5
Procedure time (minutes)		51.7 ± 15.7
Procedure complications (n)		0 (0%)

Data are numbers (n) (%) or mean values ± standard deviation (SD).

Table3. Comparison between responder group and non-responder group.

	Responder group (n=5)	Non-responder group (n=6)
Age (years)	77.6 ± 9.4	70.2 ± 12.2
Male sex (n)	3 (60%)	5 (83%)
Bilateral lesion (n)	1 (20%)	1 (17%)
Stenosis (%)	99.4 ± 0.5	84 ± 9.5
Diabetes (n)	2 (40%)	2 (33%)
Previous CAD (n)	2 (40%)	3 (50%)
Previous PAD (n)	2 (40%)	1 (17%)
Previous CVD (n)	0 (0%)	2 (33%)
RAS blockers (n)	2 (40%)	5 (83%)
Statin (n)	3 (60%)	6 (100%)
Upro/Cr>1.0g/gCr (n)	2 (40%)	2 (40%) *
Serum creatinine level (mg/dL)	4.4 ± 1.8	2.2 ± 1.0
Contrast medium/vessel (mL)	9.1 ± 2.9	8.5 ± 4.8

Data are numbers (n) (%) or mean values ± standard deviation (SD).

*n=5. One of the six did not measure urinary protein.

Figures

Figure 1

Representative case of PTR using LC-DSA.

Figure 2

sCr levels before treatment (POD0) and one month after treatment (POD30).

Legends: The solid lines were patients who decreased in sCr level $\geq 20\%$ compared to pre-treatment values. The dot lines were patients whose sCr level was unchanged (within 20% of pre-treatment values).

Figure 3

Comparison of sCr level changes between responder group(3A) and non-responder group(3B).

Legends: D (-30) means 30days before PTR. D (0) means on the day of PTR. D (30) means 30days after PTR.