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ORIGINAL ARTICLE

Efficacy and safety of endovascular therapy by diluted contrast digital subtraction angiography in patients with chronic kidney disease

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Abstract

This study was performed to evaluate the efficacy and safety of endovascular therapy (EVT) by diluted contrast digital subtraction angiography (DSA) in patients with chronic kidney disease (CKD). Patients with peripheral artery disease (PAD) often have CKD; thus, EVT carries a risk of contrast-induced nephropathy (CIN). Reducing the amount of contrast medium is, therefore, important in these patients. We developed a novel EVT method using DSA with diluted contrast medium. DSA parameters were adjusted for diluted contrast angiography (1:10 dilution), and we defined this technique as low-concentration DSA (LC-DSA). We retrospectively analyzed 122 patients with CKD [estimated glomerular filtration rate (eGFR), <45 mL/min/1.73 m^2] from June 2012 to November 2017 and classified them into two groups: EVT with diluted contrast (LC-DSA group, $n=63$) and conventional EVT (control group, $n=59$). Patients with aortoiliac lesions and those undergoing hemodialysis were excluded. The primary endpoint was the incidence of CIN as defined by an absolute increase in serum creatinine of ≥ 0.5 mg/dL or relative increase of $\geq 25\%$ 2–5 days after the procedure. The secondary endpoints were worsening renal function (defined as an eGFR reduction of $\geq 25\%$ compared with that before the procedure), the amount of contrast medium used for EVT, freedom from complications related to LC-DSA, and procedural success. The incidence of CIN was significantly lower in the LC-DSA group than control group (0.0% vs. 11.9%, respectively; $P=0.001$). The absolute eGFR increase (4.25 ± 4.7 vs. 1.24 ± 6.9, respectively; $P=0.005$) and creatinine decrease (-0.16 ± 0.2 vs. 0.007 ± 0.34, respectively; $P=0.0078$) were greater in the LC-DSA group than control group. Less contrast medium was used in the LC-DSA group than control group (30.0 ± 14.6 vs. 117.9 ± 52.8 mL, respectively; $P<0.0001$). There were no differences in the procedural success rate (100% vs. 96.6%, $P=0.23$) or complications related to LC-DSA (0.0% vs. 1.7%, $P=0.48$). Therefore, we concluded that EVT with diluted contrast DSA reduced the amount of contrast medium and incidence of CIN. This method is effective and safe for treating patients with CKD who have infrainguinal lesions.

Keywords Diluted contrast medium · Chronic kidney disease · Endovascular therapy · Contrast-induced nephropathy · Digital subtraction angiography

Introduction

The incidence of chronic kidney disease (CKD) as a comorbidity is high in patients with peripheral artery disease (PAD). Endovascular therapy (EVT) can be problematic in patients with CKD, because using large amounts of iodinated contrast medium is associated with an increased risk of contrast-induced nephropathy (CIN), progression of underlying CKD, and the need for dialysis [1]. Several methods for prevention of CIN have been reported, but no consensus has yet been reached regarding the best way to prevent this condition [2–4]. Carbon dioxide angiography is one of the most commonly used EVT methods in patients with CKD [5]. However, this method has a number of disadvantages, including fatal complications and insufficient image quality, especially in below-the-knee (BTK) lesions. To address these problems, we developed a digital subtraction angiography (DSA) program with specialized diluted contrast for EVT, which we termed low-concentration DSA (LC-DSA).

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We previously reported the effectiveness of this method for a patient with CKD [6]. Use of diluted contrast angiography can markedly reduce the amount of contrast medium used while still producing acceptable angiographs (Fig. 1). This retrospective, single-center study was performed to summarize our experience with LC-DSA, and assess the efficacy and safety of EVT using diluted contrast DSA.

Materials and methods

Patients and study design

We retrospectively analyzed 122 consecutive patients with CKD [estimated glomerular filtration rate (eGFR), < 45 mL/min/1.73 m^2] treated with EVT for infrainguinal lesions in our institute from June 2012 to November 2017. All patients had symptomatic PAD (Rutherford class 2–6) and an ankle-brachial index (ABI) of < 0.9. The patients were classified into two groups: those treated with LC-DSA (LC-DSA group, $n = 63$) and those treated with normal contrast medium (control group, $n = 59$). The patients were assigned to the LC-DSA group or control group at the operator's discretion. We started the currently used LC-DSA protocol in 2016. Patients with aortoiliac lesions were excluded because of poor DSA imaging by intestinal movement. Patients undergoing hemodialysis were also excluded, because renal function is not a concern and they can use a large amount of contrast medium.

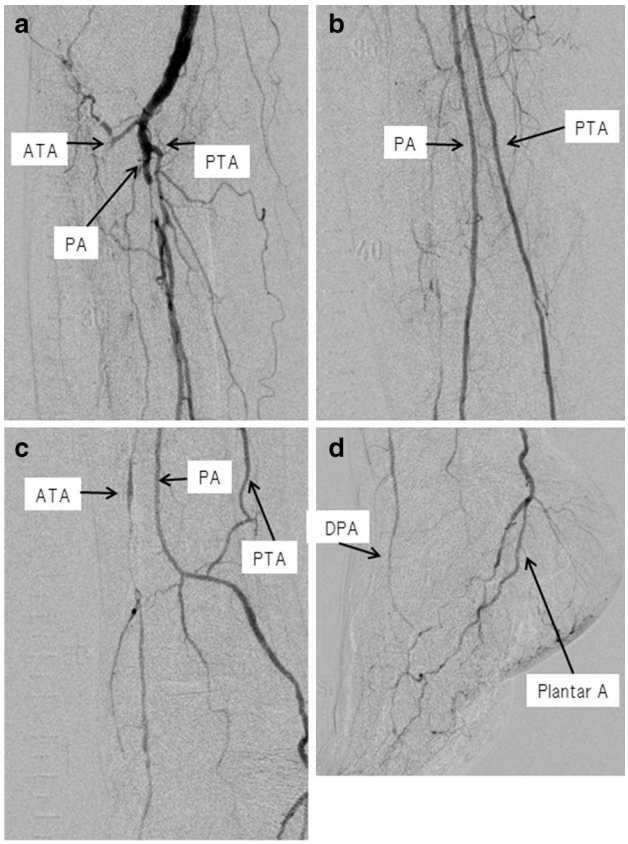

Fig. 1 Representative angiography. The injection site was the popliteal artery from a diagnostic 4-Fr catheter. The iodine contrast medium dilution rate was 10%. The exposure frame rate was three frames per second. We could clearly identify below-the-knee (BTK) and below-the-ankle (BTA) vessels and small channels (**a** proximal BTK, **b** middle BTK, **c** distal BTK, and **d** BTA). Angiography showed total occlusion of the proximal anterior tibial artery (ATA, arrow), peroneal artery (PA, arrow), and posterior tibial artery (PTA, arrow)

DSA using diluted contrast medium

An Allura Xper FD10 angiography machine (Philips, Amsterdam, The Netherlands) was used in all cases. This machine is not specific for diluted contrast angiography, and it is usually used for standard EVT and coronary interventions. We adjusted the DSA parameters, so that the dilution contrast medium was equal to 1000 Hounsfield units (HU), which is the CT number of carbon dioxide. When we adjusted the DSA parameters, we used a phantom model as a basic experiment [7]. This basic experiment showed that, by adjusting the DSA parameters and using up to a 1:10 dilution of contrast medium, we could achieve resolution almost equivalent to that of carbon dioxide DSA. The dilution rate was set to 10% based on the results of our basic experiment and the ease of manual preparation by the operator. The specialized parameters enhanced contrast, increased the sensitivity of the angiographic images, reduced the edge gain, and enlarged the edge kernel to reduce the noise (Table 1). Using diluted contrast with normal DSA settings, we could only obtain a faint DSA image (Fig. 2b); however, the use of DSA settings that emphasize the contrast made it possible to obtain a clear image even with diluted contrast medium. In addition, we obtained a sufficient angiography image not only by emphasizing the contrast but also by reducing the noise through adjustment of the edge gain and edge kernel (Fig. 2c). We defined this original DSA technique as LC-DSA. The contrast medium was iopamidol 300 mg/mL (BYSTAGE 300®; Teva Takeda Pharma Ltd., Aichi, Japan),

Table 1 Specialized parameters used for LC-DSA

	Standard DSA	LC-DSA
Sensitivity	Normal	High
Edge gain	3	1
Contrast	1.0	4.5
Edge kernel	Small	Large

DSA digital subtraction angiography, *LC-DSA* low-concentration digital subtraction angiography

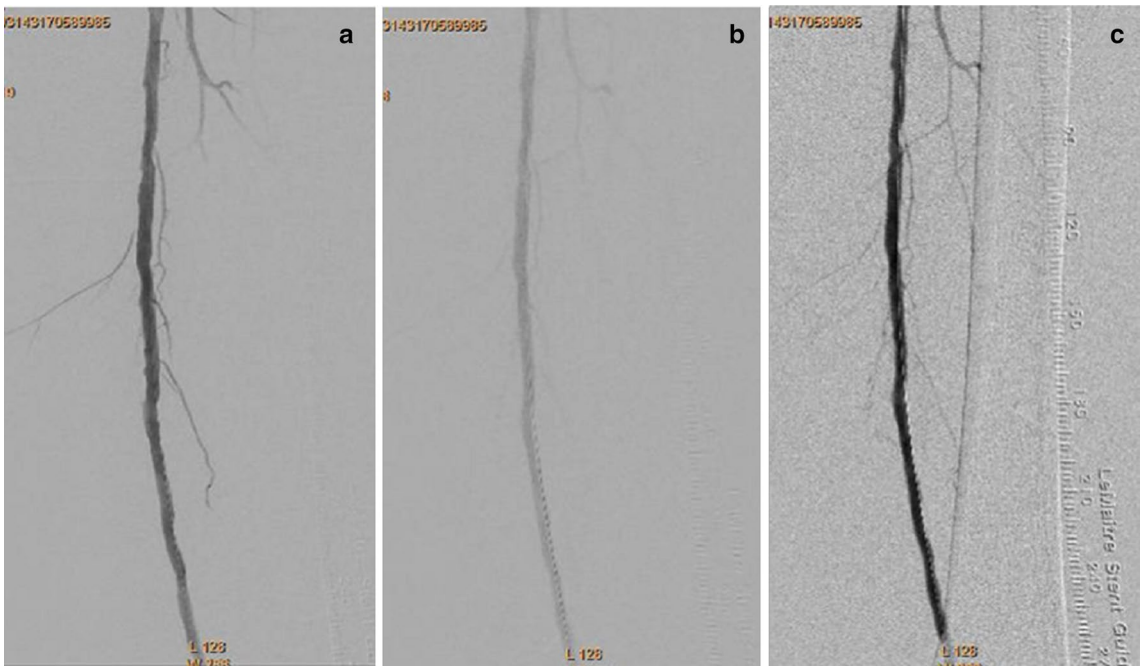

Fig. 2 Comparison between normal digital subtraction angiography (DSA) and low-concentration DSA (LC-DSA) in the superior femoral artery (SFA). **a** Use of standard contrast medium in normal DSA. **b** Use of 1:10 dilution contrast medium in normal DSA. **c** Use of 1:10 dilution contrast medium in LC-DSA. We could not clearly identify the SFA using 1:10 dilution contrast medium in normal DSA. However, the imaging quality of using 1:10 dilution contrast medium in LC-DSA was almost the same as using standard contrast medium in normal DSA

which is the same as that used in standard EVT. In the LC-DSA group, we used diluted iopamidol at 300 mg/mL manually or pre-diluted to 30 mg/mL. In the control group, we used iopamidol at 300 mg/mL.

Diluted contrast angiography technique

We used a diluted contrast solution consisting of 10 mL of contrast medium and 90 mL of 5% glucose. All injections were performed manually with a volume of 5–10 mL. Quality evaluation of LC-DSA angiograms was performed by each operator. If the image was unacceptable, we obtained another angiogram by adjusting the contrast solution concentration or used another angiographic method (Fig. 3). Some patients in the LC-DSA group underwent both standard digital angiography and DSA.

Procedural protocol

Intravenous hydration using normal saline at 1.0 mL/kg/h was started in all patients at least 12 h before the procedure and continued for at least 12 h after the procedure. Aspirin and clopidogrel or cilostazol were started at least 24 h before the procedure. All procedures were performed with local anesthesia. After sheath insertion from the ipsilateral or contralateral femoral artery, at least 5000 units of heparin was administered. If the guidewire passed the lesion, pre-dilatation was performed using a balloon of the appropriate size. We used bare nitinol stents for femoropopliteal lesions in some patients with a residual pressure gradient of > 20 mmHg, residual stenosis of > 30%, or flow-limiting dissection. However, only balloon angioplasty was performed for BTK lesions.

Study endpoints

The primary endpoint was the incidence of CIN (defined as an absolute increase in the serum creatinine level of ≥ 0.5 mg/dL or relative increase of ≥ 25% measured 2–5 days after the procedure). The secondary endpoints were worsening renal function (defined as an eGFR reduction of ≥ 25% compared with that before the procedure), the amount of contrast medium used for EVT, freedom from complications related to LC-DSA, and procedural success. Procedural success was defined as < 30% residual stenosis. Complications were defined as any morbidity during the follow-up period. We defined reshot as having to retake the angiogram, because the image was unclear.

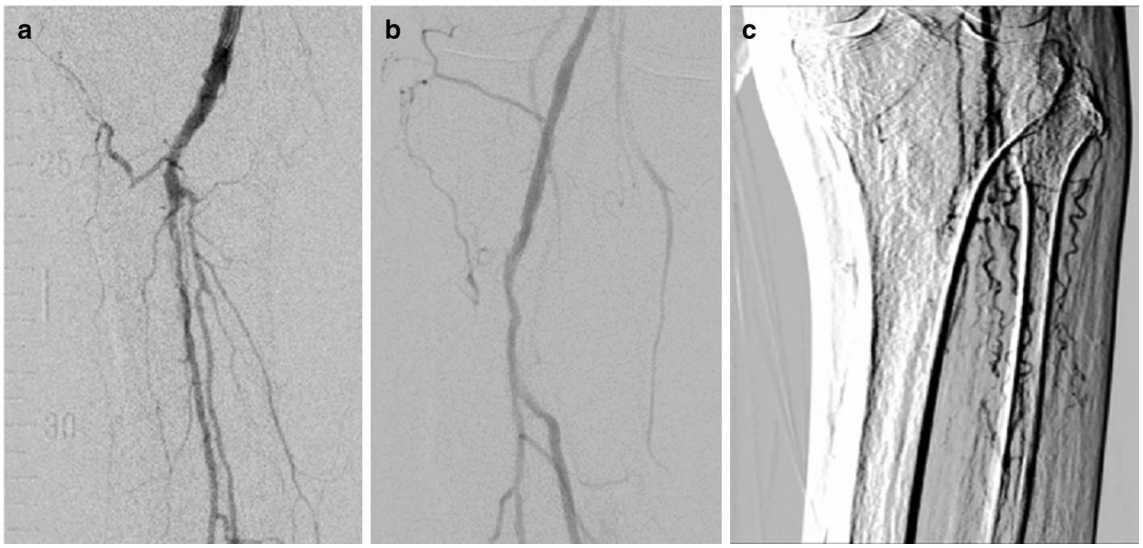

Fig. 3 Comparison of excellent, average, and poor low-concentration digital subtraction angiography (LC-DSA) imaging. **a** Excellent LC-DSA image. We could identify target vessels and small branch vessels well. **b** Average LC-DSA image. We could evaluate main target vessels. **c** Poor LC-DSA image. We could not evaluate target vessels

Follow-up

The baseline serum creatinine concentration and eGFR were measured 1 day before the procedure from blood samples, and the follow-up serum creatinine concentration and eGFR were measured 2–5 days after the procedure. The day on which blood was taken was chosen at the operator's discretion (2–5 days after the procedure). Clinical evaluation was performed within 14 days after the procedure. We investigated clinical symptoms, the ABI, renal function, the total amount of contrast medium, and the cumulative dose area product (DAP).

Statistical analysis

All analyses were performed using JMP version 13.0 (SAS Institute, Cary, NC). The results are expressed as mean ± standard deviation. We used the unpaired Student's *t* test to compare the values between two groups. Categorical variables were analyzed by Fisher's exact test. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Table 2 Patients' clinical characteristics

	LC-DSA ($n=63$)	Control ($n=59$)	*P* value
Age, years	74.9 ± 10.7	74.9 ± 9.4	0.75
Male	50 (79.4)	35 (59.3)	0.016
BMI, kg/m^2	23.4 ± 0.59	23.9 ± 0.65	0.61
HT	60 (95.2)	57 (96.6)	0.7
DM	56 (88.9)	45 (76.3)	0.06
DL	50 (79.4)	47 (79.7)	0.97
CAD	41 (65.1)	31 (52.5)	0.16
CVD	25 (39.7)	8 (13.6)	0.0009
Smoking	43 (68.3)	28 (47.5)	0.02
CLI	35 (55.6)	40 (67.8)	0.14
Number of lesions	1.44 ± 0.71	1.49 ± 0.82	0.96
F–P lesion	48 (76.2)	47 (79.7)	0.67
BTK lesion	20 (31.8)	17 (28.8)	0.72
CTO	41 (65.1)	34 (57.6)	0.39

Data are presented as mean ± standard deviation or *n* (%)

BMI body mass index, *HT* hypertension, *DM* diabetics, *DL* dyslipidemia, *CAD* coronary artery disease, *CVD* cerebrovascular disease, *CLI* critical limb ischemia, *F-P* femoropopliteal, *BTK* below the knee, *CTO* chronic total occlusion

Results

Patients and lesions

There were almost no differences in the baseline clinical characteristics between the two groups (Table 2). The body mass index was not significantly different between the two groups, and differences in individual patients' body shape did not seem to affect the image quality. The proportions of male patients and patients with cerebrovascular disease were higher in the LC-DSA group than control group. In both groups, the incidence of critical limb ischemia was > 50% and that of chronic total occlusion was > 50%. The number of lesions per patient was about 1.4 in both groups. There were almost no significant differences in the types of treated lesions between the groups. The prevalence of

femoropopliteal lesions and BTK lesions was almost same between the two groups.

Primary and secondary endpoints

Table 3 summarizes the results related to renal function and the procedural characteristics. The mean serum creatinine level decreased from 2.09 ± 1.2 to 1.94 ± 1.1 mg/dL in the LC-DSA group after the procedure, while that in the control group increased from 1.53 ± 0.7 to 1.54 ± 0.8 mg/dL ($P = 0.0078$). The absolute decrease in serum creatinine was greater in the LC-DSA group than control group. In addition, the absolute increase in the eGFR was higher in the LC-DSA group than control group (4.25 ± 4.7 vs. 1.24 ± 6.9, respectively; $P = 0.005$). The incidence of CIN was significantly lower in the LC-DSA group than the control group (0.0% vs. 11.9%, respectively; $P = 0.001$). In addition, the rate of worsening renal function was lower in the LC-DSA group than control group (7.94% vs. 38.9%, respectively; $P < 0.001$).

The ABI was increased in both groups after the procedure. The procedural success rate was similarly high in both groups. Less contrast medium was used in the LC-DSA group than control group ($P < 0.0001$). In the LC-DSA group, the total amount of contrast medium used was only 30.0 ± 14.6 mL, and the amount of contrast medium per shot was 1.38 ± 0.85 mL. The quality of diluted angiography was maintained. Moreover, the reshot rate was very low (1.09 ± 1.85). We could perform EVT for almost all LC-DSA shots in the LC-DSA group. In addition, there were no complications related to LC-DSA. The cumulative DAP was greater in the LC-DSA group than control group ($P = 0.009$).

Discussion

The results of the present study suggest that DSA with diluted contrast medium is very effective to prevent progression of renal dysfunction, because the total volume of contrast medium used is markedly less than that in the standard EVT procedure. The rates of CIN and progressive renal dysfunction were lower in the LC-DSA group in this study. In addition, the absolute decrease in the serum creatinine level and the absolute increase in the eGFR were greater in the LC-DSA group than control group. These results are consistent with the fact that CIN could be reduced. Improvements in the serum creatinine level and eGFR may also have beneficial effects on hydration during the procedure, but both groups had similar hydration conditions. The preoperative renal function was certainly different between the two groups. We also considered that LC-DSA prevented the deterioration of renal function despite the poor renal conditions. The follow-up duration of ≤ 14 days might be too

Table 3 Pre- and post-procedural estimated glomerular filtration rate and creatinine level, absolute change from preprocedural level, incidence of contrast-induced nephropathy and worsening renal function, and procedural characteristics

	LC-DSA ($n = 63$)	Control ($n = 59$)	P value
Pre eGFR, mL/min/1.73 m^2	29.4 ± 8.5	34.8 ± 8.5	0.0095
Post eGFR, mL/min/1.73 m^2	33.6 ± 13.7	35.9 ± 10.6	0.75
Absolute change in eGFR, mL/min/1.73 m^2	4.25 ± 4.7	1.24 ± 6.9	0.005
Pre-creatinine, mg/dL	2.09 ± 1.2	1.53 ± 0.7	0.0006
Post-creatinine, mg/dL	1.94 ± 1.1	1.54 ± 0.8	0.056
Absolute change in creatinine, mg/dL	− 0.16 ± 0.2	0.007 ± 0.34	0.0078
CIN	0 (0.0)	7 (11.9)	0.001
Worsening renal function	5 (7.94)	23 (38.9)	< 0.0001
Pre ABI	0.68 ± 0.17	0.62 ± 0.18	0.08
Post ABI	0.87 ± 0.19	0.85 ± 0.2	0.58
Total contrast volume, mL	30.0 ± 14.6	117.9 ± 52.8	< 0.0001
Procedural success, %	100	96.6	0.23
Complications, %	0.0	1.7	0.48
Volume per shot, mL	1.38 ± 0.85	7.08 ± 3.04	< 0.0001
Number of shots	23 (19–33)	18 (9–28)	0.0028
Number of reshots	0 (0–1)	0 (0–0)	< 0.0001
Reshot rate, %	3.8 ± 6.2	0.14 ± 0.7	< 0.0001
Fluoro time, min	37.8 ± 22.8	52.0 ± 38.6	0.1
Cumulative DAP, Gy cm^2	40.1 ± 25.7	32.8 ± 31.2	0.009

Data are presented as mean ± standard deviation, *n* (%), or median (interquartile range) unless otherwise indicated

eGFR estimated glomerular filtration rate, *CIN* contrast-induced nephropathy, *ABI* ankle-brachial index, *DAP* dose area product

short to define the transition of renal function. However, we evaluated the occurrence of CIN (the primary endpoint) within 5 days after the procedure, because, according to prior studies, evaluation of the incidence of CIN is usually performed using data within 5 days [8, 9]. We considered that the evaluation of short-term clinical results and perioperative complications within 14 days after the procedure was sufficient.

The total volume of contrast medium was clearly less in the LC-DSA group than control group (about one-third less on average). Although the contrast medium was diluted by 10 times, it was not one-tenth of the volume. The control group had many DA (digital angiography) images and few DSA images, and a direct comparison of DSA was not performed. In addition, angiography at locations other than the treatment site was not performed in some patients because of preservation of renal function, and an intravascular ultrasound (IVUS)-guided approach was used in some patients in the control group. However, the most important finding is that LC-DSA clearly reduced the amount of contrast medium.

The procedure success rate in the LC-DSA group was high and similar to that in the control group. The quality of diluted angiography was acceptable, because the reshot rate was very low and we could perform EVT for almost all LC-DSA shots in all patients in the LC-DSA group. In the LC-DSA group, there was no case in which we could not perform the procedure and had to change to normal DSA. Furthermore, there were no complications related to diluted contrast angiography. Because LC-DSA only decreases the amount of contrast medium used in the standard procedures, special complications related to the procedure are unlikely to occur. These results support the effectiveness and safety of LC-DSA.

Several methods for preventing CIN have been reported, such as the use of hydration, sodium bicarbonate, hemofiltration, N-acetylcysteine, ascorbic acid, nicorandil, and iloprost [8–13]. And some risk factors of CIN have been reported [14]. However, no consensus regarding the optimal method has yet been reached. CIN occurred in 5.0–18.5% of patients even with application of these preventive methods. The rate of CIN was clearly lower in the present study than described in the previous reports [15, 16]. The only effective means of preventing CIN is to reduce the amount of contrast medium [17]. Laskey et al. reported that the recommended amount of contrast agent used to preserve renal function was less than twice the GFR value [18]. Using LC-DSA, it was possible to reliably reduce the amount of the contrast medium, and in our study, the amount of contrast medium was less than that value in almost all cases.

Our novel method of DSA with diluted contrast medium does not require specialized angiography equipment; we used our daily-use angiography machine in all LC-DSA cases. However, it is necessary to adjust the parameters of DSA for very high-sensitivity angiographic images with enhanced image contrast and reduced edge strength to obtain high resolution. Adjustment of this DSA parameter basically involves control of contrast and noise. Noise is common to all angiography machines, so a specific angiography machine is not required. We usually prepare diluted contrast medium consisting of 10 mL of contrast medium and 90 mL of 5% glucose, and manually inject an average of 5–10 mL. We usually use iopamidol 300 mg/mL as a contrast medium; if another type of contrast medium such as iopamidol 370 mg/mL is used, the dilution concentration may slightly change. The previous reports have described computed tomography angiography using contrast medium diluted about 1:3–1:4 [19]. To our knowledge, however, no reports have described intra-arterial DSA with diluted contrast medium. This study suggests that there are benefits to the use of diluted contrast angioplasty for patients with renal dysfunction.

Methods to reduce the amount of contrast medium include carbon dioxide angioplasty and IVUS-guided approaches [20]. Carbon dioxide angioplasty can be performed effectively for EVT in patients with CKD [21]. However, several serious complications related to this technique have been reported [22]. In addition, the imaging quality tends to be poor in BTK lesions because of the presence of gas bubbles [23]. Furthermore, patients often feel severe pain and move their legs during the procedure. With the use of LC-DSA, however, patients are often able to remain still, because there is no pain associated with contrast medium injection. The IVUS-guided approach can also reduce the amount of contrast medium required [24], but it is difficult to determine the degree of blood flow, branch vessels, and some collaterals using IVUS. In addition, the use of IVUS in BTK lesions is limited, because the IVUS catheter cannot pass these lesions.

LC-DSA has some disadvantages. First, DSA imaging is highly susceptible to motion artifacts because of its high sensitivity. The main reason for reshot in the present study was motion artifacts. We herein applied this method for infrainguinal disease, but it is often difficult to apply this method to aortoiliac lesions because of intestinal movement. Second, the radiation dose tends to be higher than that of standard digital angiography. The cumulative DAP was greater in the LC-DSA group than control group in the present study. However, the value seemed to be acceptable, because it was similar to that in complex EVT or standard coronary interventions [25].

At present, we usually use LC-DSA for infrainguinal EVT in patients with CKD (eGFR of < 45 mL/min/1.73 m^2) to preserve their renal function.

Limitations

This was a retrospective, nonrandomized, single-center study. Thus, the number of patients was small, and selection bias cannot be ruled out. The procedures in both groups were not comparable at the same time. Because the patients in the LC-DSA group were treated more recently than those in the control group, there is a possibility that improvements in the operator's skill and the development of devices might have affected the procedure success rate and the complication rate. However, no significant differences in the clinical or procedural characteristics were found between the two groups. The follow-up duration might have been too short for a thorough discussion of the transition of renal function. The amount of iodinated contrast medium depended on the physician. In addition, no core laboratory was available. These factors may have affected the results.

Conclusions

EVT with diluted contrast DSA is a safe and effective method for treating patients with CKD who have infrainguinal lesions. The LC-DSA method may be useful for treating patients with CKD and preventing CIN.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

Research ethics All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients.

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