



Cilostazol plus clopidogrel in the prevention of in-stent stenosis after vertebral artery origin stenting in gout patients: three case reports

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Abstract

It is unclear whether cilostazol instead of aspirin in combination with clopidogrel could prevent in-stent thrombosis in patients with a history of gout undergoing vertebral artery origin stenting. Three men (age range, 58–74 years) were diagnosed with acute ischaemic stroke or transient ischaemic attack. Vertebral artery origin stenosis was visible by computed tomographic angiography or digital subtraction angiography. Four bare metal stents were placed in the vertebral artery origin. The patients were administered 100 mg cilostazol orally twice a day and 75 mg clopidogrel orally once a day perioperatively and 100 mg cilostazol orally twice a day was administered indefinitely after 3 months. No in-stent stenosis was observed in all of these patients during a follow-up period up to 19 months. Cilostazol plus clopidogrel has the potential to become an alternative to standard dual antiplatelet therapy in vertebral artery origin stenting. A high-quality clinical trial is needed to verify these preliminary findings.

Keywords

Cilostazol, gout, vertebral artery origin, stent

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Introduction

Aspirin plus clopidogrel is recommended as the standard dual antiplatelet therapy (DAPT) to prevent in-stent thrombosis in percutaneous coronary intervention (PCI) and carotid artery stenting.¹ However,

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aspirin can significantly reduce the clearance rate of uric acid and increase the serum uric acid level in elderly patients;² and the risk of gout recurrence increases by approximately two-fold in patients taking low-dose aspirin on two consecutive days.³ Therefore, for gout patients that are going to undergo intervention therapy, other antiplatelet drugs that replace aspirin are needed.

Vertebral artery origin stenosis (VAOS) is an important aetiology of ischaemic stroke in the posterior cerebral circulation.⁴ Endovascular intervention therapy for VAOS has been widely used in clinical practice, although in-stent restenosis (ISR) in VAOS is more common than that in other arteries such as the coronary or carotid artery.⁵ In a study of patients undergoing percutaneous coronary intervention, the cilostazol group receiving cilostazol plus clopidogrel had less ISR than the aspirin group receiving aspirin plus clopidogrel.⁶ However, to the best of our knowledge, there has been no report describing the risk of ISR in VAOS stenting patients with gout taking cilostazol instead of aspirin in combination with clopidogrel. This current case study reports the imaging and clinical outcomes of three patients with a history of gout undergoing VAOS stenting and taking cilostazol plus clopidogrel as DAPT.

Case reports

This case report describes a retrospective analysis of three consecutive patients that underwent VAOS implantation between January 2018 and July 2019 at the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China. All intervention procedures were performed via a transfemoral route under local anaesthesia without conscious sedation. Systemic anticoagulation was initiated by intravenous administration

of a bolus of 2000–3000 U heparin. The type of stent was chosen at the discretion of the interventionist. Written informed consent to treatment was obtained before intervention procedures.

The study met the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University (reference number: 2015-412) and written informed consent was obtained from all patients or their legally authorized representatives for publication of their data before discharge. All patient details have been anonymized.

Case 1

A 74-year-old male with a history of hypertension and gout that complained of dizziness, aphasia and an unsteady gait for 3 days was admitted to hospital on 5 January 2018. Magnetic resonance imaging (MRI) showed multiple acute cerebral infarctions in the right brainstem and computed tomographic angiography (CTA) indicated a severe VAOS. The patient was administered 100 mg aspirin orally once a day and 75 mg clopidogrel orally once a day. Subsequently there was swelling and pain in the left hand joints, which was considered to be the recurrence of gout. The aspirin was replaced with 100 mg cilostazol orally twice a day. According to the opinion of the endocrinologist, 200 mg CELEBREX[®] orally once a day, 40 mg febuxostat orally once a day and 500 mg sodium bicarbonate orally three times a day were given for 1 week. Please note that the other two patients were treated with the same regimen. On day 7 after hospitalization, digital subtraction angiography (DSA) showed a bilateral stenosis of 90% of the VAOS based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (Figures 1A and 1E). The NASCET

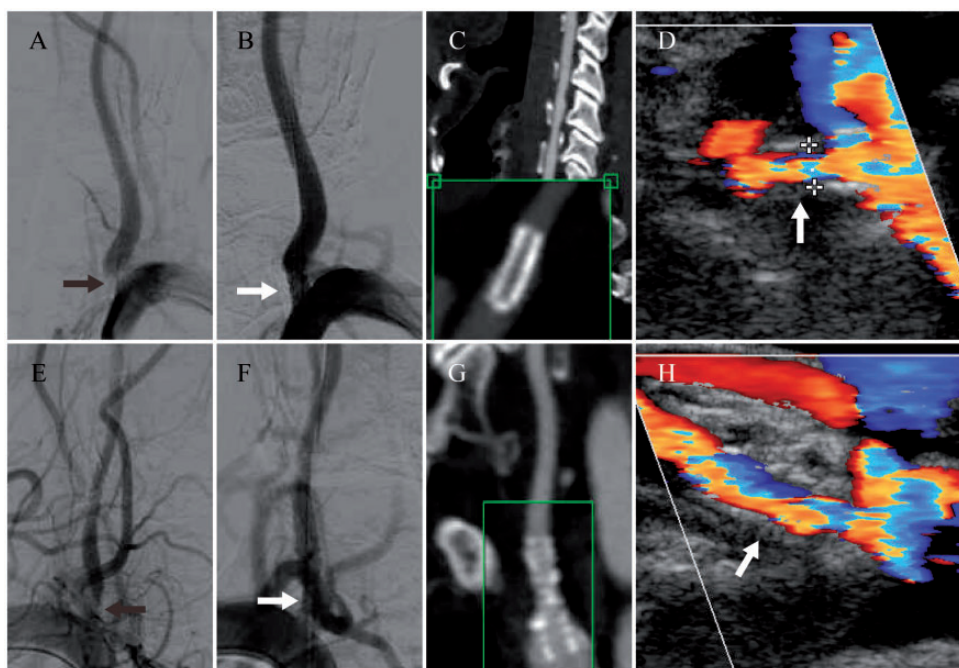


Figure 1. A 74-year-old male (case 1) with a history of hypertension and gout complained of dizziness, aphasia and an unsteady gait for 3 days was admitted to hospital. (A) On day 7 after hospitalization, digital subtraction angiography (DSA) showed a left vertebral artery origin stenosis (VAOS) (arrow); (B) stent implantation of the left VAOS (arrow); (C) computed tomographic angiography (CTA) at 3 months of the left VAOS; (D) colour Doppler ultrasonography at 19 months of the left VAOS (arrow); (E) on day 7 after hospitalization, DSA showed a right VAOS (arrow); (F) stent implantation of the right VAOS (arrow); (G) CTA at 3 months of the right VAOS; (H) colour Doppler ultrasonography at 19 months of the right VAOS (arrow). The colour version of this figure is available at: <http://imr.sagepub.com>.

method calculates the extent of stenosis using the following formula: percentage stenosis = $(1 - [\text{narrowest diameter}/\text{normal distal diameter}]) \times 100$.⁷ A 4.0 mm × 12 mm RX Herculink Elite stent (Abbott Vascular, Santa Clara, CA, US) and a 4.0 mm × 18 mm Apollo balloon-mounted stent (MicroPort, Shanghai, China) were placed in the left and right vertebral artery origin, respectively (Figures 1B and 1F). The patient was discharged after 3 days and continued to take 100 mg cilostazol orally twice a day plus 75 mg clopidogrel orally once a day for 3 months; and then received 100 mg cilostazol orally twice day alone indefinitely. At 3 months after discharge, a cervical CTA showed no ISR (Figures 1C

and 1G); and at 19 months after discharge colour Doppler ultrasound also showed no ISR (Figures 1D and 1H). During the follow-up, there were no adverse clinical events such as stroke, angina pectoris or myocardial infarction, or death.

Case 2

A 70-year-old male with a history of gout that had syncope, aphasia and left hemiparesis for 7 days was admitted to hospital on 23 July 2018. Acute cerebral infarction in the right temporal lobe and occipital lobe was visible on MRI. The patient was administered 100 mg aspirin orally once a day and 75 mg clopidogrel orally once a

day; and several days later the aspirin was changed to 100 mg cilostazol orally twice a day and 75 mg clopidogrel orally once a day due to a gout attack in the left foot. On day 12 after hospitalization, DSA showed that the stenosis rate of the right VAOS was 80% based on the NASCET method (Figure 2A) and a 4.0 mm × 24 mm Promus Element stent (Boston Scientific, Natick, MA, USA) was implanted (Figure 2B). This patient was discharged after 5 days and continued to take 100 mg cilostazol orally twice a day and 75 mg clopidogrel orally once a day for 3 months. Then, 100 mg cilostazol orally twice a day was given alone indefinitely. At 3 months after

discharge, colour Doppler ultrasonography showed no ISR at the site of stent implantation (Figure 2C); and at 12 months, the CTA showed no ISR too (Figure 2D). During the follow-up period there were no adverse clinical events.

Case 3

A 58-year-old male with a history of hypertension and gout presented to the hospital on 6 February 2019 because of repeated attacks of dizziness in the past 4 years. CTA showed severe stenosis of the left VAOS. The patient was administered 100 mg aspirin orally once a day and 75 mg clopidogrel orally once a day. On

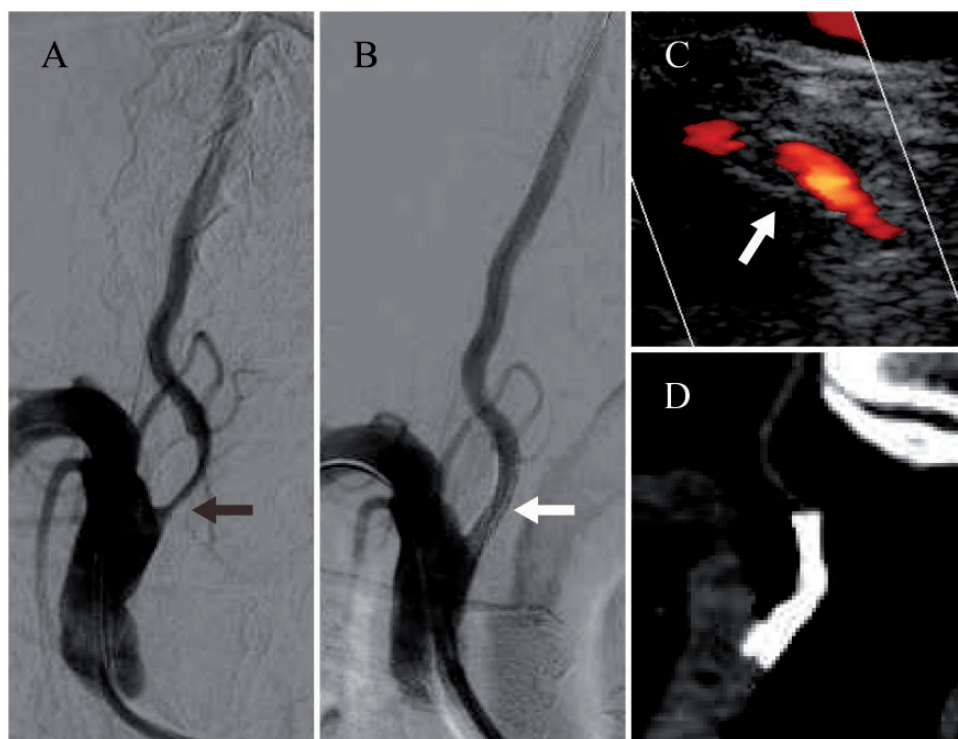


Figure 2. A 70-year-old male (case 2) with a history of gout that had syncope, aphasia and left hemiparesis for 7 days was admitted to hospital. (A) On day 12 after hospitalization, digital subtraction angiography showed a right vertebral artery origin stenosis (VAOS) (arrow); (B) stent implantation of the right VAOS (arrow); (C) colour Doppler ultrasonography at 3 months of the right VAOS (arrow); (D) computed tomographic angiography at 12 months of the right VAOS. The colour version of this figure is available at: <http://imr.sagepub.com>.

day 9 after hospitalization, DSA showed a local eccentric plaque in the left VAOS with a stenosis rate of 60% based on the NASCET method (Figure 3A). A 4.5 mm × 12 mm RX Herculink Elite stent (Abbott Vascular) was placed (Figure 3B). On day 3 after the operation, there was a gout attack in the left toe. The aspirin was changed to 100 mg cilostazol orally twice a day. After hospital discharge, the patient continued to take 100 mg cilostazol orally twice a day and 75 mg clopidogrel orally once a day for 3 months. Then, 100 mg cilostazol orally twice a day was given alone indefinitely. Grey-scale ultrasonography at 1 month and CTA at 6 months showed no ISR in the left VAOS (Figures 3C and 3D).

There were no adverse clinical events during the 9-month follow-up.

Discussion

Cilostazol is a phosphodiesterase inhibitor with antiplatelet activity.⁸ A previous study demonstrated that the continued use of cilostazol for 12 weeks could lower uric acid levels in patients with impaired glucose tolerance or type 2 diabetes.⁹ In addition, cilostazol effectively reduced P2Y₁₂ reaction units in clopidogrel-resistant patients and increased platelet inhibition.¹⁰ A meta-analysis that summarized seven retrospective studies that included 1297 patients that had undergone carotid artery stenting

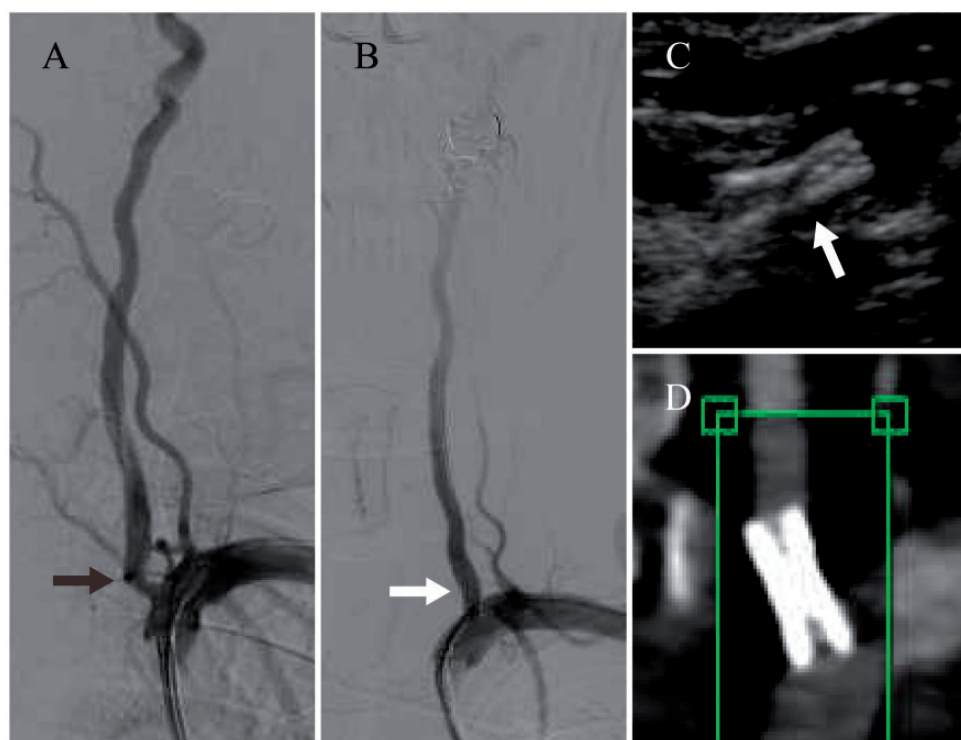


Figure 3. A 58-year-old male (case 3) with a history of hypertension and gout presented to the hospital because of repeated attacks of dizziness in the past 4 years. (A) On day 9 after hospitalization, digital subtraction angiography showed a local eccentric plaque in the left vertebral artery origin stenosis (VAOS) (arrow); (B) stent implantation of the left VAOS (arrow); (C) grey-scale ultrasonography of the left VAOS (arrow) at 1 month; (D) computed tomographic angiography of the left VAOS at 6 months.

found that cilostazol plus any other antiplatelet drugs (including aspirin, clopidogrel, ticlopidine) had a lower ISR rate than the non-cilostazol group.¹¹ There was no significant difference found in myocardial infarction, stroke or death at 30 days and during follow-up (mean 20 months) between the two groups, which was consistent with the role of cilostazol in patients with PCI.¹¹ Another study that evaluated cilostazol plus clopidogrel as an alternative to standard DAPT in aspirin-intolerant patients with PCI reached similar conclusions.⁶ However, the role of cilostazol in combination with non-aspirin antiplatelet drugs in VAOS stenting remains to be verified. In this case report, during a follow-up period up to 19 months after surgery, there was no ISR in patients with gout taking cilostazol and clopidogrel after VAOS stent implantation. These preliminary findings suggest that cilostazol plus clopidogrel has the potential to become an alternative to standard DAPT in patients undergoing VAOS stenting. These findings need to be verified in large randomized controlled trials that could compare the efficacy and safety between aspirin or cilostazol plus clopidogrel in the prevention of ISR after VAOS stenting.

In conclusion, the findings of these three case studies suggest that a combination of cilostazol and clopidogrel may prevent ISR in patients with a history of gout undergoing VAOS stenting. Further studies are needed to confirm the efficacy and safety of this dual antiplatelet treatment regimen in preventing ISR after stent implantation in VAOS.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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