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Case Report

Successful outcome of intra-arterial tissue plasminogen activator treatment for patient with acute middle cerebral artery occlusion beyond the 6-hour time window: case series report of 3 middle-aged and aged patients

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Abstract: Local intra-arterial recombinant tissue plasminogen activator (IA rt-PA) is an effective treatment for acute middle cerebral artery (MCA) occlusion with a time window of 6 hr. However, the outcomes of IA rt-PA treatment beyond the 6-hour time window are largely unknown. Here we reported three successful cases of intra-arterial thrombolysis by using small dose of rt-PA in patients with acute MCA occlusion over the 6-hour time window. Three patients had sudden onset of symptoms. Emergency angiography showed the complete occlusion of M1 segment of the MCA in the three cases. Neurological examination showed severe neurological dysfunction at admission (National Institutes of Health Stroke Scale [NIHSS] graded as 12, 11 and 13, respectively). After local thrombolysis treatment with rt-PA (total dose of 6 mg, 10 mg and 6 mg, respectively), the occluded MCA gradually recanalized. Postoperative CT showed no hemorrhagic transformation in Case 1 and Case 2, and asymptomatic intracranial hemorrhage in Case 3. All three patients had a good recovery with slight paresis and mild aphasia after 2 weeks (NIHSS graded as 0, 1, and 1, respectively). The mRS of the three patients was 0 at day 90. Our reported suggested that low dose of rt-PA arterial thrombolysis may be a feasible treatment option for acute MCA occlusion in middle-aged and aged patients, even beyond the 6-hour window.

Keywords: Middle cerebral artery (MCA) occlusion, recombinant tissue plasminogen activator (IA rt-PA), intra-arterial thrombolysis (IAT), ischemic stroke, recanalization, case report

Introduction

Ischemic stroke remains one of the leading causes of death around the world [1], and is caused most commonly by occlusion of middle cerebral artery (MCA) [2]. Untreated acute MCA occlusion reportedly results in 20% of mortality and more than 70% of long-term disability [3]. It has been shown that time to treatment is a crucial prognostic factor for acute stroke [4]. Intravenous administration of recombinant tissue plasminogen activator (IV rt-PA/alteplase) is currently approved by the US Food and Drug Administration and is the first-line therapy for acute ischemic stroke (AIS) within 3 hr after the onset of symptoms [5]. However, due to the narrow time window, only 3-10% of AIS patients admitted to emergency department are eligible for standard IV rt-PA therapy [6]. Intra-arterial thrombolysis (IAT) is an alternative treatment for AIS with an optimal time window of 6 hr [7]. The longer treatment time window is a potential advantage of IAT as compared with IV rt-PA [8]. Nevertheless, even extended to 6 hr, this time window remains not practical for many AIS patients due to the limited health care services. Studies showed that only 5%-13% of AIS patients are within the window of 3 to 6 hr [8]. Base on this suggested time window, majority studies of IAT focus on the outcomes of patients treated within 6 hr after onset. Hence, the outcomes of IA rt-PA treatment beyond the 6-hour time window are largely unknown. The purpose of this study was to report three successful

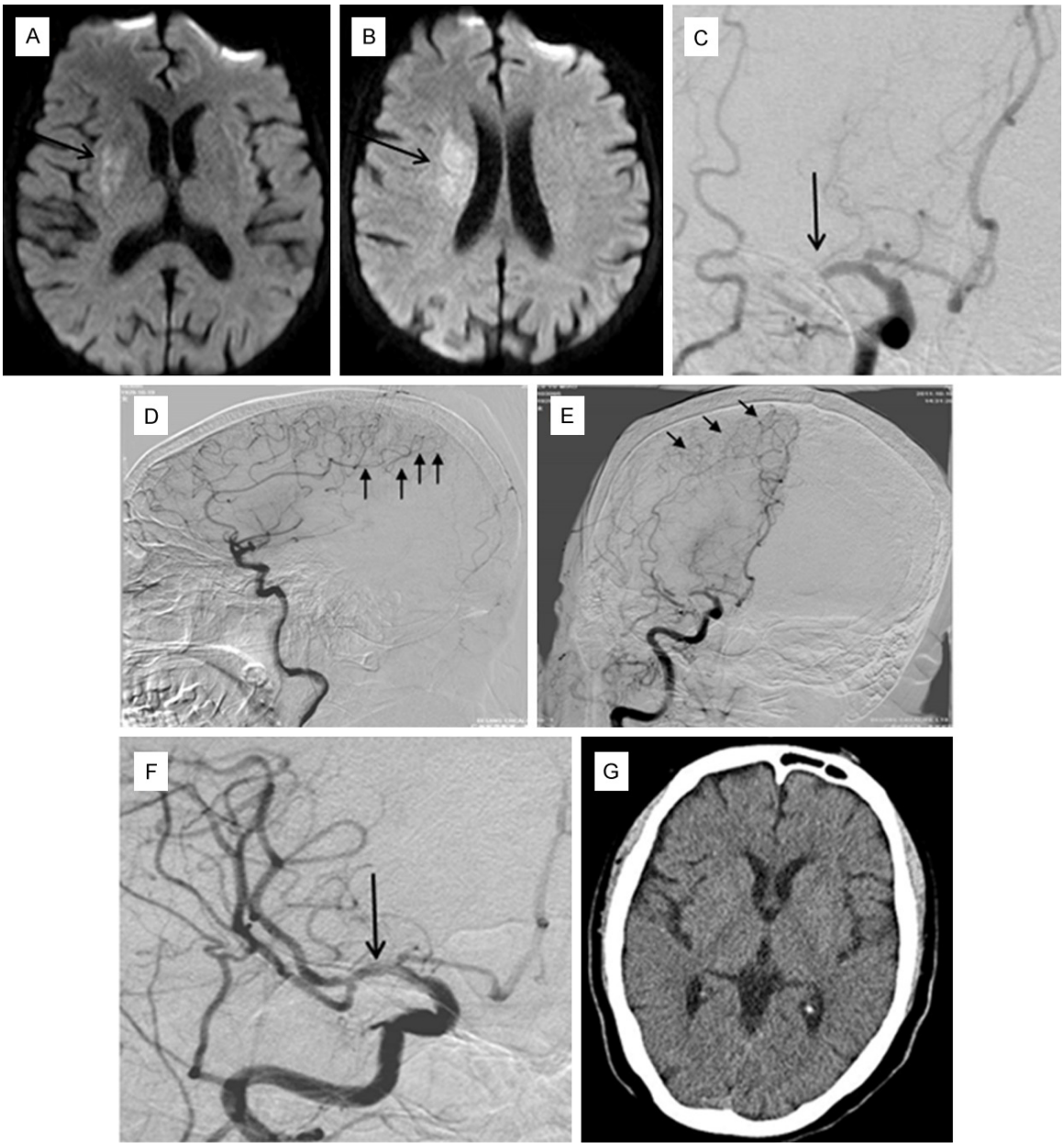

Figure 1. Radiographic and angiographic images of Case 1. (A) DWI showed a fresh infarction in the right basal ganglia area (black arrow). (B) DWI showed a fresh infarction in the right corona radiate (black arrow). MR brain DWI image before thrombolysis. (C) M1 segment of the right MCA was subtotally occluded (black arrow). Lateral (D) and anterior (E) cerebral angiographic images showed compensatory leptomeningeal arteries from anterior cerebral artery (black arrows). (F) The occluded MCA was recanalized (black arrow). (G) Postoperative CT showed no hemorrhagic transformation.

cases of intra-arterial thrombolysis by using small dose of rt-PA in patients with acute MCA occlusion over the 6-hour time window in our center.

Case report

Informed consent was obtained from patient 3 and the family relatives of patients 1 and patient 2. This study was approved by the institutional review board of the First Affiliated Hospital of Guangzhou Medical University. All patients received computed tomography (CT) or magnetic resonance imaging (MRI) scan before IAT treatment to exclude intracranial hemorrhage and to confirm the diagnosis of MCA occlusion. The disability status and neurological function were assessed with modified

Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) at admission, 2 weeks and 90 days, respectively.

Case 1

An 82-year-old female had sudden onset of hemiplegia and global aphasia. The patient had medical history of hypertension for 5 years, diabetes for 9 years. Neurological examination showed aphasia, paralysis of the left central facial muscle and tongue, and a Babinski sign on the left. The symptoms became worse approximately 4.5 hr after onset: blood pressure elevated to 220/98 mmHg, both eyes staring to the right, the left upper limb muscle strength graded as level 0, the left lower muscle strength graded as level 2 and NIHSS graded as 12. Laboratory tests showed a blood glucose level of 8.3 mmol/L (normal range 3.9-6.1).

Diffusion-weighted imaging (DWI) showed a fresh infarction area in the right corona radiate and basal ganglia (**Figure 1A** and **1B**). MR angiography (MRA) presented right MCA occlusion. Cerebral angiography confirmed that M1 segment of the right MCA was subtotally occluded (**Figure 1C**). Before IAT, cerebral collateral circulation compensation of occluded MCA was evaluated. Angiographic images showed compensatory leptomeningeal arteries from anterior cerebral artery supplying the territory of MCA (**Figure 1D** and **1E**). IAT therapy was initiated at 6.75 hr after symptoms onset. Six mg rt-PA in multiple boluses at 1 mg/min was administrated via a 6F introducer catheter. The angiography at 5 min after surgery showed the occluded MCA gradually recanalized (**Figure 1F**). Postoperative examinations showed that muscle strength of left limb graded as level 5, NIHSS graded as 2, and the angiographic recanalization of the symptomatic artery graded as TIMI III. Postoperative CT showed no hemorrhagic transformation (**Figure 1G**). The patient fully recovered from IAT therapy after 2 weeks, with the NIHSS graded as 0, and the mRS graded as 0 at day 90.

Case 2

A 57-years-old male had slurred speech and weakness on the left limb for 38 hr, with a medical history of cerebral infarction for 9 years. Neurological examination at admission showed mixed aphasia, the left limb muscle strength graded as level 4, the left Babinski sign is negative, and NIHSS graded as 4. Cranial MR showed multiple fresh cerebral infarctions in the right frontal, arietal and temporal lobe and basal ganglia area. The symptoms became worse at 2 hr after admission. Neurological examination showed paralysis of the left central facial muscles and tongue, left limb muscle strength graded as level 0, Babinski sign (+), and NIHSS graded as 11.

DWI showed fresh infarctions in the right basal ganglia area and the right corona radiate (**Figure 2A** and **2B**). Cerebral angiography showed that M1 segment of the right MCA was subtotally occluded, and compensatory leptomeningeal arteries from anterior cerebral artery supplying the territory of MCA (**Figure 2C**). IAT therapy was initiated at 42 hr after symptoms onset. Six mg rt-PA was administered directly into the thrombus. At 5 min after surgery, the occluded MCA gradually recanalized (**Figure 2D**), and the angiographic recanalization of the symptomatic artery was graded as TIMI III. Patient's symptoms diminished significantly 24 hr after surgery, with left limb muscle strength graded as level 5 and NIHSS graded as 1. Postoperative CT showed no hemorrhagic transformation (**Figure 2E**). At 2 weeks, the NIHSS was 1, and the mRS was 0 at day 90.

Case 3

A 74-year-old male was admitted due to slurred speech and weakness of right limb for 3 hr. The past medical history included atrial fibrillation, hypertension and postoperative percutaneous transluminal coronary angioplasty. Neurological examination showed aphasia, paralysis of right central facial muscle and tongue, right upper limb muscle strength graded as level 5, right lower muscle strength graded as level 5, a Babinski sign on the right. The symptoms worsen at 6 hr after onset: Neurological examination showed mixed aphasia, paralysis of the right central facial muscle, right upper limb muscle strength graded as level 0, right lower limb muscle strength graded as level 2, a Babinski sign on the right, NIHSS 13. Laboratory tests showed blood glucose was 6.8 mmol/L. Electrocardiography (ECG) showed an atrial fibrillation.

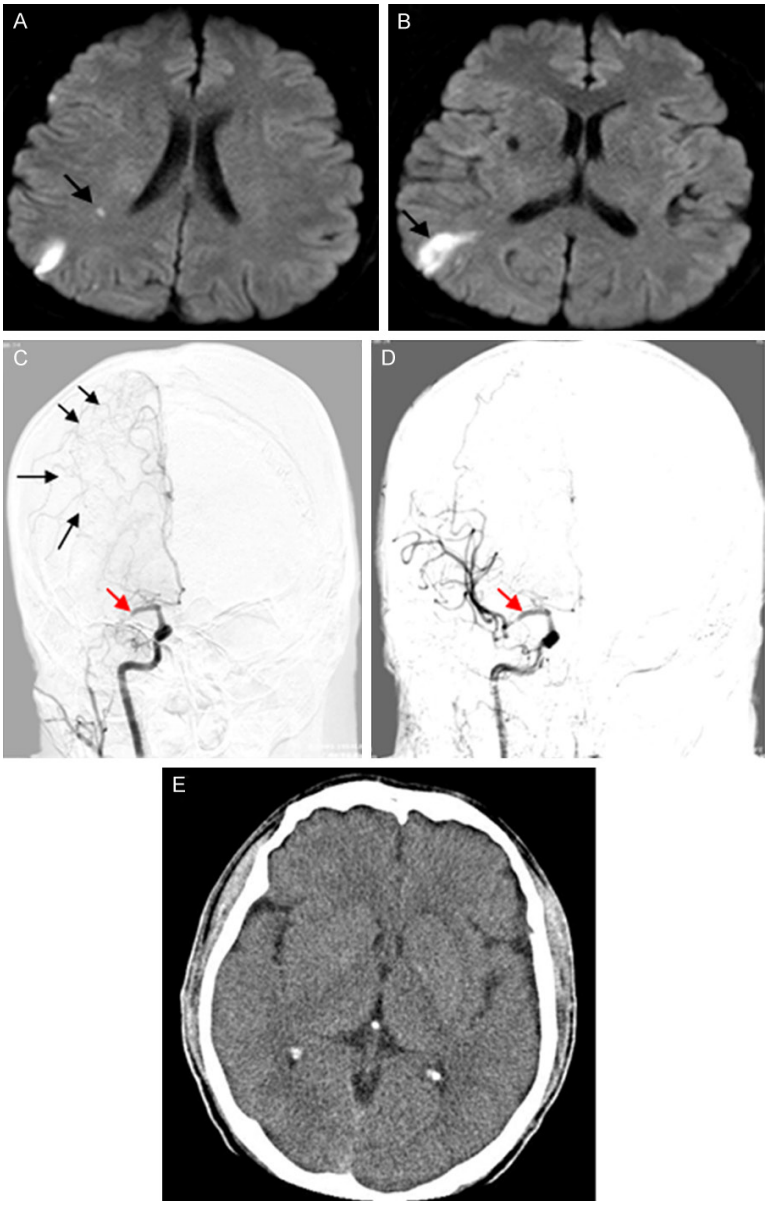

Figure 2. Radiographic and angiographic images of Case 2. A. DWI showed a fresh infarction in the right basal ganglia area (black arrow). B. DWI showed fresh infarctions in the right corona radiate (black arrow), MR brain DWI image before thrombolysis. C. Cerebral angiographic mages showed the occluded right MCA (red arrow) and compensatory leptomeningeal arteries from anterior cerebral artery (black arrows). D. Postoperative angiographic mages showed the recanalized right MCA (red arrow). E. Postoperative CT showed no hemorrhagic transformation of brain.

Cranial DWI+MRI+MRA showed fresh infarctions in left corona radiate and right occipital area (**Figure 3A** and **3B**), and the M2 segment of the left MCA was blocked. Cerebral angiography confirmed that M1 segment of the left MCA was occluded (**Figure 3C**). Preoperative angiographic images showed compensatory leptomeningeal arteries from anterior cerebral artery (**Figure 3D** and **3E**). IAT therapy was initiated at 9 hr after symptoms onset. Three thousand U of heparin and 6 mg rt-PA were locally administered. Due to the tortuosity in the internal carotid artery, microcatheter can not reach M1 segment of the left MCA. rt-PA were then administered through a 5F vethralcather. The angiography at 5 min after surgery showed the occluded MCA gradually recanalized (**Figure 3F**), with the recanalization of the symptomatic artery was assessed as TIMI III. At 24 hr after surgery, patient's symptoms diminished significantly, with left limb muscle strength graded as level 5 and NIHSS graded as 1. Cranial CT showed the left external capsule and basal ganglia hemorrhaged (**Figure 3G**), then broken into ventricles, indicating bleeding after thrombolysis.

Neurological examination at 2 weeks revealed paralyses of mild central facial muscle, upper right muscle strength graded as level 5, lower right muscle strength graded as level 5, and NIHSS graded as 1. Cranial CT showed that the hemorrhage lesions of the left basal ganglia were absorbed. The mRS was 0 at day 90.

Discussion

Compared to IV rt-PA therapy, IAT therapy has several potential advantages, including angiographic planning to customize therapy, localized injection, more complete recanalization, less thrombolytic drug used and a longer therapeutic time window of up to 6 h after symptom onset [9, 10]. However, in clinical practice,

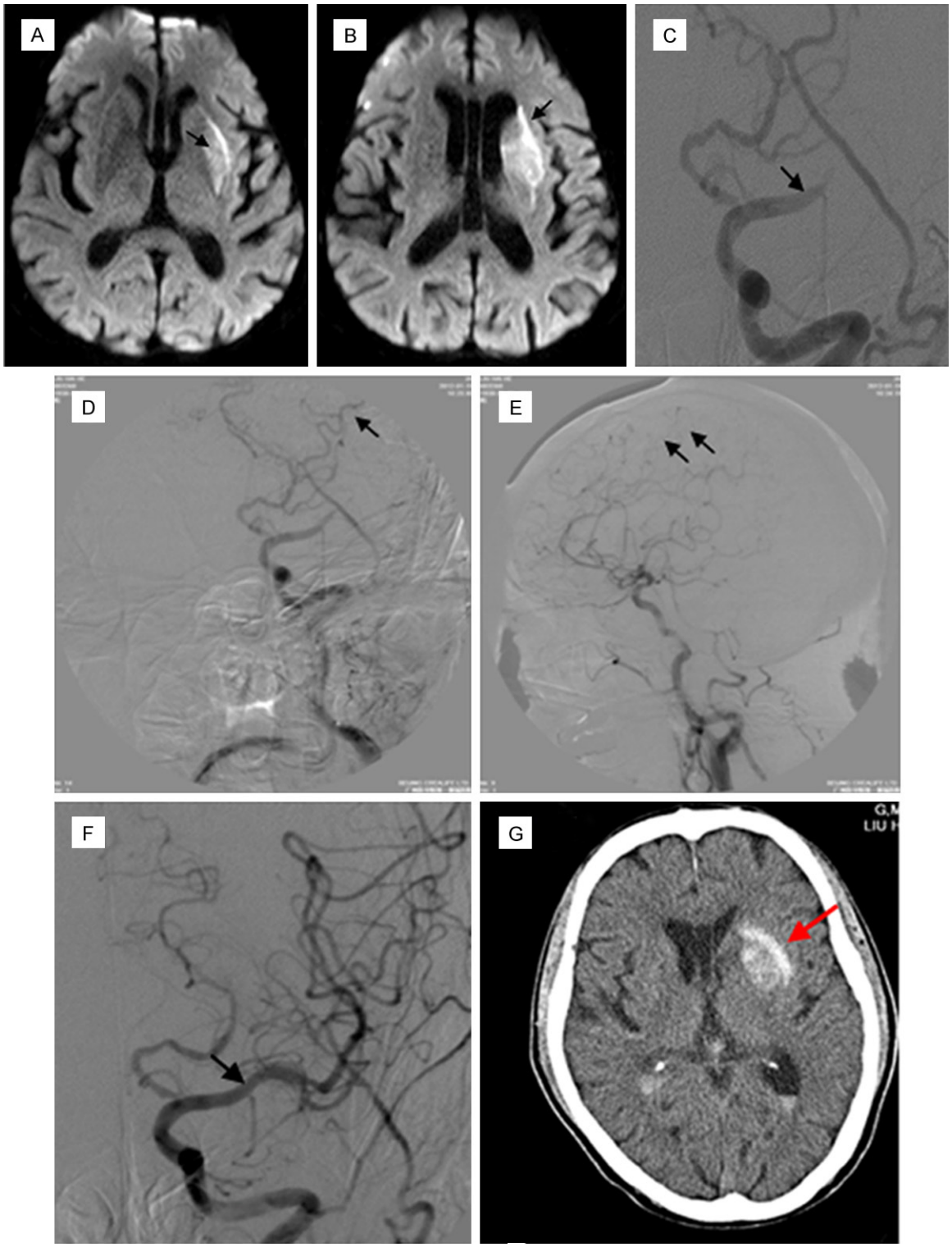

Figure 3. Radiographic and angiographic images of Case 3. (A) DWI showed fresh infarctions in the left basal ganglia area (black arrow). (B) DWI showed fresh infarctions in the corona radiate (black arrow). (C) M1 segment of the left MCA was subtotal occluded (black arrow). Lateral (D) and anterior (E) cerebral angiographic images showed compensatory leptomeningeal arteries from anterior cerebral artery (black arrows). (F) Occluded MCA recanalized (black arrow). (G) Postoperative CT showed asymptomatic basal ganglia hemorrhage (red arrow).

there are still many AIS patients presented to emergency department not eligible to IAT therapy due to exceeding the suggested 6-hour time window. Coster *et al*. have reported two

cases of successful intra-arterial thrombolysis beyond the accepted 6-hour time window (10 h and 11 h after onset, respectively) in two young patients (<23 year-old) [11]. Here we reported three middle-aged and aged patients with MCA occlusion successfully treated with IAT beyond the 6-hour time window. At admission, all the 3 patients had already exceeded the therapeutic time window for IAT, thereby the treatment options are limited. We chose low dose localized intra-arterial rt-PA treatment. All three patients obtained good recanalization of the MCA, and recovered well at 2 weeks after surgery (NIHSS 0, 1 and 1, respectively), except for the asymptomatic bleeding in Case 3. Recurrent stroke was not found with 1 year follow up after IAT treatment.

All the three cases had severe symptoms at admission. The disease progression in Case 1 and Case 2 may be associated with the thrombus progression of the MCA. Patient in Case 3 had medical history of atrial fibrillation and coronary heart disease. It has been shown that late treatment for AIS leads a greater risk of bleeding after recanalization [12]. In addition, studies have suggested that rt-PA is related to hemorrhagic transformation [13], and IAT therapy has the risk for intracranial hemorrhage [10]. High doses of rt-PA can increase the risk of bleeding [14]. Base on the above considerations, we chose to use a minimal dose of rt-PA. The doses of rt-PA for the 3 cases were 6 mg, 10 mg and 6 mg, respectively, which are far below the maximum dose of 22 mg used in other study [15]. Recanalization of the MCA could be achieved in all the 3 patients, and they have a good 1-year therapeutic outcome. Our report indicated that small dose of rt-PA can efficiently induce artery recanalization, which may be beneficial to patients with severe stroke. However, the dose of rt-PA for artery thrombolysis still needs to be individualized. It has been suggested that after rt-PA therapy, recanalization alone is not the guarantee to achieve an excellent recovery [3]. Since collateral circulation compensation has been shown to be the main recovery factor [16], the good clinical outcomes of these three patients may be associated with good compensatory leptomeningeal arteries from anterior cerebral artery observed in the angiographic images.

In summary, our report suggested that low dose of rt-PA arterial thrombolysis may be a feasible treatment option for acute MCA occlusion in middle-aged and aged patients, even beyond the 6-hour window. A large sample study is needed to verify the findings of the current report.

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Disclosure of conflict of interest

None.

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