



A case of cerebral infarction during a hemodialysis procedure successfully treated with recombinant tissue plasminogen activator

Wei Han¹ · Tsutomu Sakurada¹ · Rina Hachisuka¹ · Sayaka Kuroya¹ · Hirofumi Sumi¹ · Shigeki Kojima¹ · Takeshi Okamoto¹ · Yugo Shibagaki¹ · Yoko Tsuchihashi² · Kenji Isahaya² · Naoshi Sasaki² · Yasuhiro Hasegawa²

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Abstract

Thrombolytic therapy is an effective treatment for acute ischemic stroke and provides benefits and improvements that lead to better neurological outcomes. However, thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA) in hemodialysis (HD) patients is limited because HD patients have a higher risk of bleeding. We report a case of a 75-year-old HD patient who presented with sudden aphasia during HD treatment. She was brought to the hospital for treatment for infarction. Following thrombolytic therapy, we achieved re-opening without complications. To our knowledge, no report has been published describing the patients who had a stroke during a maintenance HD session and were treated with r-tPA successfully. Although the number of HD patients treated with r-tPA is small and requires further investigation, thrombolytic therapy can be an alternative option. After weighing the risks and benefits and assessing each patient carefully, the use of r-tPA should be considered, even in HD patients.

Keywords Hemodialysis · Stroke · Cerebral infarction · Recombinant tissue plasminogen activator

Introduction

Treatment for cerebral infarction has been developed over time. In the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (r-tPA) Stroke Study, a better neurological outcome was confirmed 3 months after treatment [1]. A subsequent randomized controlled trial, the European Cooperative Acute Stroke Study III, reported favorable outcomes following administration of r-tPA intravenously within 4.5 h of onset of symptoms [2]. In Japan, administration of r-tPA within 4.5 h of symptom onset has been used since 2012. This treatment is given after evaluation of neurological findings, determination of risk of hemorrhage from past medical history of hemorrhage or

infarction, and use of medications such as antiplatelet or anticoagulation drugs [3]. However, thrombolytic therapy may increase the risk for bleeding, including intracranial hemorrhage (ICH), as a potential serious complication [1, 2]. r-tPA is less likely given to the patients on hemodialysis (HD) in Japan, because chronic kidney disease (CKD) and HD patients are considered to have a higher risk of hemorrhage [4, 5]. Also, according to the Japanese guideline for r-tPA administration, severe renal failure falls into the category of administering carefully. Bleeding diathesis is due to uremia, microvascular damage, and anticoagulation during HD treatment. Uremia results in dysfunction of intrinsic and extrinsic factors, causing impaired platelet aggregation and dysfunction [6], and microvascular vulnerability contribute to ruptures following reperfusion therapy. We present a case of an HD patient who experienced a stroke event during her HD therapy, and who was successfully treated with r-tPA without complications.

✉ Tsutomu Sakurada
sakurada@marianna-u.ac.jp

¹ Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao Miyamae-ku, Kawasaki, Kanagawa, Japan

² Division of Neurology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao Miyamae-ku, Kawasaki, Kanagawa, Japan

Case report

A 75-year-old woman was brought to the emergency department due to sudden-onset aphasia. Her prior activities of daily living were normal, with no cognitive disorders. She had been on regular maintenance HD treatment beginning at 1:20 p.m. Anticoagulation during dialysis therapy was performed with induction with 750 units of heparin, and was followed by continuous 500 units per hour. She experienced a decrease in blood pressure (BP) around 2:54 p.m., when she became unable to speak. Upon suspicion of a stroke event, HD was stopped and she was brought to the emergency department. At the time of arrival by ambulance, she presented with no paralysis but demonstrated aphasia. Figure 1 shows the alteration of systolic and diastolic blood pressure during HD.

At the time of admission, she was taking D-sorbitol 10 mL/day (as a laxative), simvastatin 5 mg/day, cinacalcet 25 mg/day, calcium carbonate 1500 mg/day, ferric citrate hydrate 750 mg/day, rebamipide 300 mg/day, mecobalamin 1500 µg/day, rabeprazole 10 mg/day, alfacalcidol 0.25 µg/day, and sodium polystyrene sulfonate 6.54 g/day. She did not drink any alcohol or smoke cigarettes. She also had no allergies.

Her past medical history included hyperlipidemia, gastroesophageal reflux disease, sigmoid colon and rectal adenoma followed by endoscopic mucosal resection, and end-stage kidney disease due to autosomal dominant polycystic kidney disease. She had begun peritoneal dialysis 14 years before, and had started combined therapy with peritoneal dialysis and HD 9 years before, and she had fully switched to HD 7 years before this current presentation.

The physical exam revealed a height of 142.5 cm and weight of 42.8 kg. Her vital signs were body temperature 36.9 °C, BP 179/92 mmHg, regular heart rate 80 bpm, respiratory rate 19/min, and oxygen saturation of arterial blood measured with a pulse oximeter 95% (room air). Her Glasgow Coma Scale was E3V1M5, and she was able to answer to questions by nodding and could follow simple

orders but could not speak out. Neurologic findings revealed pupils 3/3 mm, pupils equally round and reactive to light and accommodation, extraocular movements were intact, and cranial nerves II–XII were intact. She had neither paralysis nor sensory deficits. We could not assess her coordinated movements because she could not follow some orders. In summary, her neurologic deficit was global aphasia. No other findings were noted for her chest and abdomen. Her Manual Muscle Test was also normal.

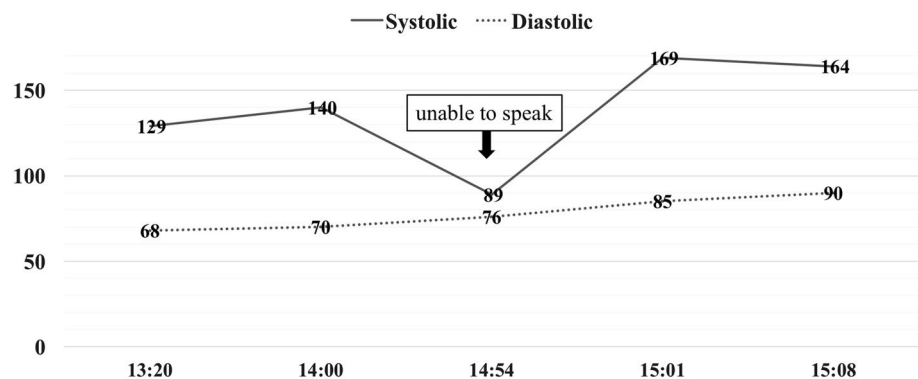
The routine laboratory indices are shown in Table 1. Electrocardiogram at admission revealed sinus rhythm and QS pattern was found in lead II, III, and aVF. Her chest X-ray showed a chest thoracic ratio of 66% and an enlarged heart. Because the electrocardiogram change led us to suspect that she had an ischemic lesion, during hospital stay, transthoracic echocardiography (TTE) was performed. TTE revealed an ejection fraction of 22%, and hypokinesis in the posterior and inferior walls with diastolic dysfunction. Mitral valve regurgitation due to tethering was also noted. Since she had a large lesion in M1 that occluded both the anterior and posterior arteries, and because she had low cardiac function, even though she had no atrial fibrillation, infarction due to embolism of cardiac source was considered the most likely diagnosis.

Table 1 Laboratory findings at admission

WBC	6400/µL	D-Dimer	4.0 µg/mL	UA	4.2 mg/dL
Hb	11.7 g/dL	Total protein	6.2 g/dL	CRP	0.31 mg/dL
Plt	180,000/µL	Albumin	3.5 g/dL	T-chol	187 mg/dL
PT-INR	1.01	Cr	5.64 mg/dL	BNP	2980 pg/mL
APTT	28.7 s	BUN	47.9 mg/dL		

WBC white blood cells, Hb hemoglobin, Plt platelets, PT-INR normalized prothrombin time-international ration, aPTT activated partial thromboplastin time, Cr creatinine, BUN blood urea nitrogen, UA uric acid, CRP C-reactive protein, T-chol total cholesterol, BNP brain natriuretic peptide

Fig. 1 Transition of blood pressure during HD. The solid line shows systolic pressure and dotted line shows diastolic pressure



Computed tomography and magnetic resonance imaging (MRI) was performed. The MRI located an acute cerebral infarction in the left middle cerebral artery (MCA) zone, M1 zone, where both the anterior and posterior branches were occluded (Fig. 2a, b). r-tPA was indicated, as the stroke event happened 2 h and 15 min before presentation and she had no cerebral hemorrhage or any contraindication for r-tPA administration. She was given Alteplase 26.1 mL as r-tPA (0.6 mg/kg when calculated with a body weight of 45 kg according to the Japanese guideline for the management of stroke 2015 [3]). The National Institutes of Health Stroke Scale (NIHSS) score just before administration was 5, and the score became 4 at 15 min after administration.

On day 2, after computed tomography confirmed the absence of a cerebral hemorrhage 24 h after r-tPA, she was started on heparin 10,000 units per day due to suspicion of embolism. On day 3, which was her usual maintenance HD, we started on low-efficiency dialysis. HD was started with a blood flow of 120 mL/min, and cellulose triacetate was used as a dialyzer (small membrane with an area of 1.10 m²). Ultrafiltration was also done gradually and cautiously so that she would not develop dehydration or hypovolemia. Her HD condition was gradually increased back to the baseline level that was performed at her previous HD clinic. Meanwhile, her aphasia improved, and she was able to repeat words on day 4.

In addition, due to suspicion of ischemia from her TTE findings, she was started on aspirin on day 4. Repeated MRI on day 17 after onset showed re-opening of the

posterior branch but no change in infarct lesions (Fig. 3a, b). At the same time, her language functional evaluation gradually improved. On day 19, she was able to speak simple words and on day 39, although she had some verbal paraphasia, daily communication was possible.

She underwent cardiac angiography and that showed chronic total occlusion in the left circumflex artery and 99% ischemia in the right coronary artery. Percutaneous coronary intervention was planned, but because she was still in the acute phase of stroke, it was postponed. Her anticoagulation therapy by heparin for infarction was planned to be changed to warfarin on day 19. While we started warfarin, and adjusted the dose according to prothrombin time-international normalized ratio (PT-INR), heparin was stopped on day 23 when PT-INR was in the targeted range. While she waited for elective percutaneous coronary intervention, she was recommended to undergo dual-antiplatelet therapy for her coronary lesion, and clopidogrel was added. Not only was she taking two antiplatelet medications but she was also taking anticoagulant medication, the fact that she was an HD patient with bleeding tendency, and because she did not have atrial fibrillation, after weighing risks and benefits, for the fear of developing hemorrhagic complications warfarin was stopped on day 38. In-patient rehabilitation continued. She was discharged on day 69 after admission with significant speech improvement, and she is still undergoing rehabilitation for full recovery. The clinical course of the patient is shown in Fig. 4.

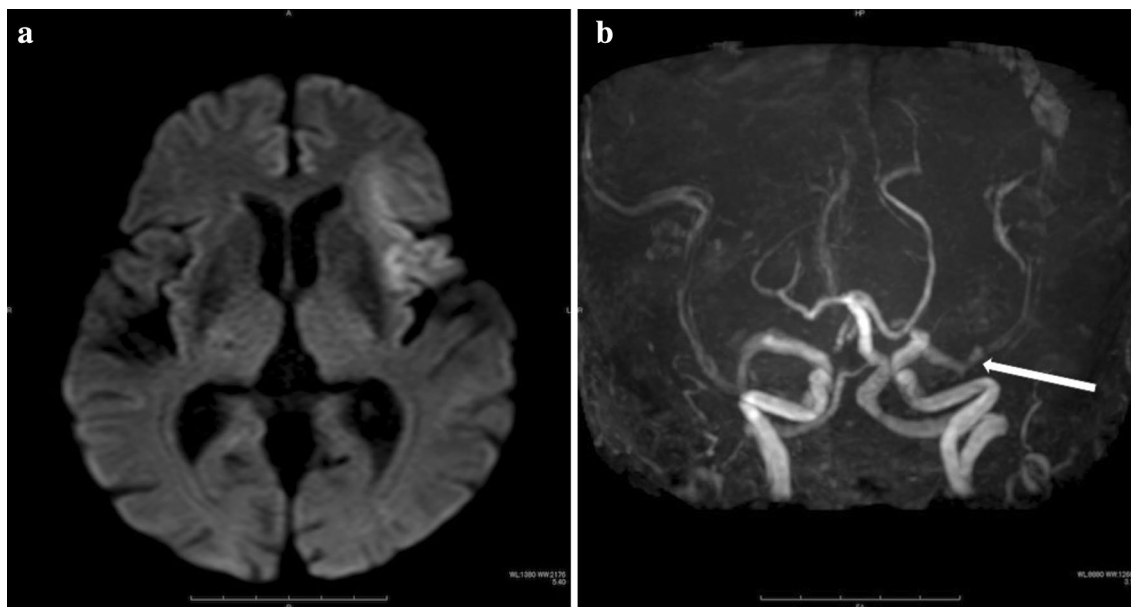


Fig. 2 MRI and magnetic resonance angiography (MRA) taken on the day of admission, revealing acute cerebral infarction in the left middle cerebral artery (MCA) zone. A high signal at MCA zone

on diffuse weighted image (DWI) (a). MRA showing MCA artery including M1 zone, where both the anterior and posterior branches are occluded (b)

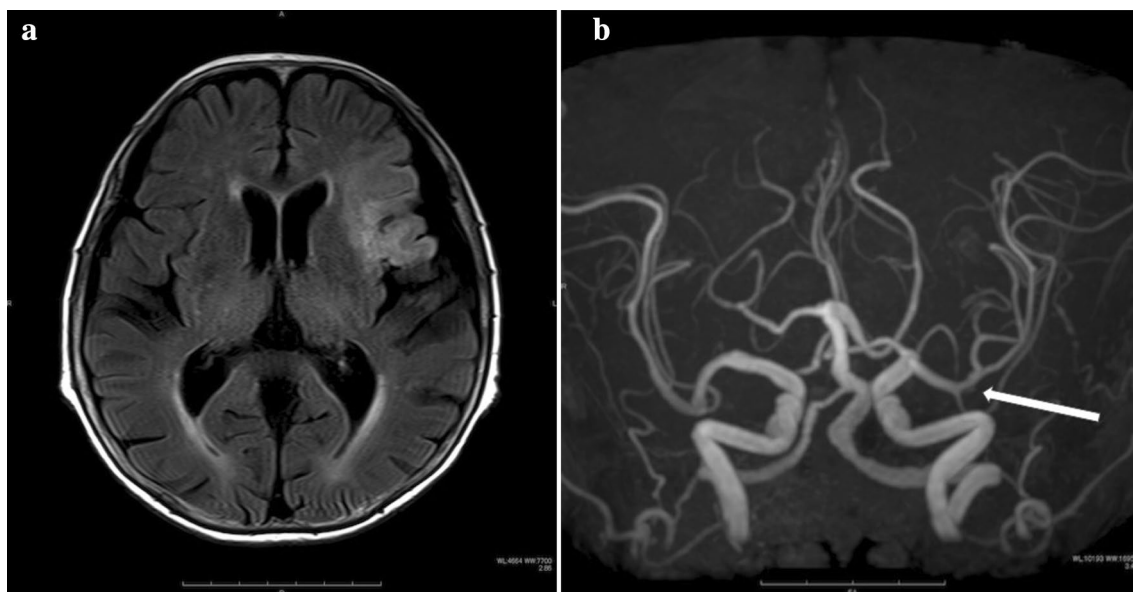


Fig. 3 MRI and MRA taken on 17th day of admission, revealing high signal at MCA zone on T2 fluid-attenuated inversion recovery (FLAIR) image (a). MRA showing re-opening of the MCA artery including both anterior and posterior branches (b)

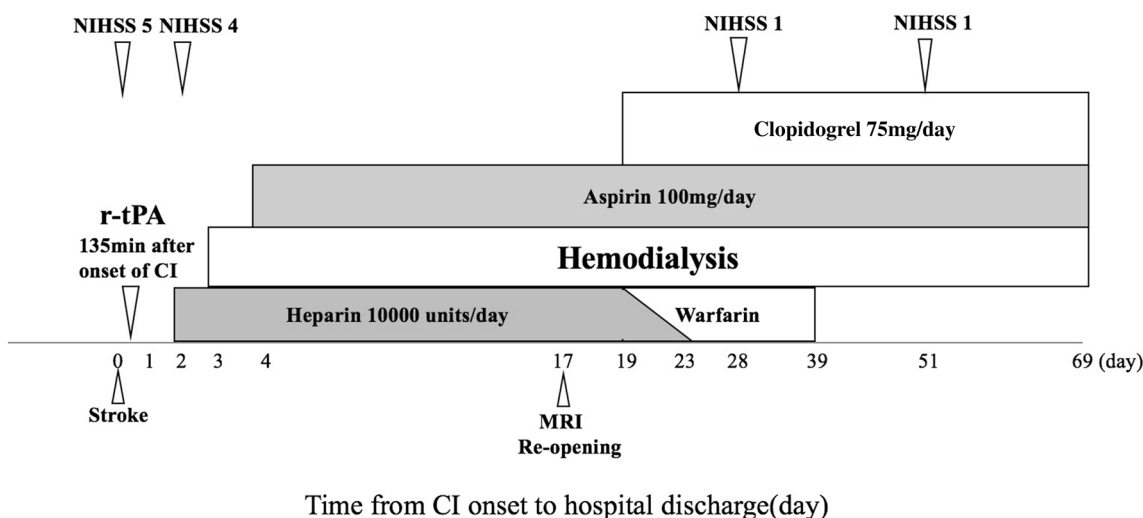


Fig. 4 Time course of clinical events

Discussion

Our case is unique because the stroke event occurred during HD treatment requiring heparin use. Since major guidelines recommend that the activated partial thromboplastin time be in the normal range if heparin has been given within the previous 48 h [1], HD patients are less likely to be candidates because of anticoagulation during HD. However, there was no aPTT prolongation or contraindication when r-tPA was administered. Her aPTT was

not extended may have been due to insufficient anticoagulation. Although her membrane did not coagulate during HD, a shortage of heparin use as the cause of infarction cannot be ruled out as the activated clotting time and aPTT were not measured during HD. The thrombolytic therapy with r-tPA has been reported to manage better clinical, neurological outcomes and activity of daily living [1, 2], as in this case, improvement in her aphasia and re-opening of the lesion. The re-opening of the lesion is presumed to be effects of r-tPA, since physiologically heparin only prevents thrombus propagation [7], and there

are no meta-analysis data supporting heparin being useful. However, there have been few cases that achieved partial and complete lysis of thrombus by heparin, it is difficult to rule out the effect of heparin use from day 2 playing a partial role in re-opening in this patient [8]. Aspirin use also has not been found to be associated with re-opening of lesions [9]. Furthermore, heparin and aspirin use for the purpose of achieving re-opening has not been suggested in the guidelines.

In means of treating cerebral infarction, administration of r-tPA plays a pivotal role; however, it comes with risk of hemorrhage, especially in HD patients with bleeding tendency [4, 5]. SAMURAI study, a multicenter collaboration conducted in Japan in 2011, among 578 patients including 186 patients with renal dysfunction, revealed that renal dysfunction was significantly associated with more ICH events, poor outcomes, and higher mortality [4]. The latest report of 15,191 CKD patients with ischemic stroke given r-tPA, confirmed neither significant ICH was associated, but in-hospital mortality was higher in patients with CKD that increased with more severe renal dysfunction [10]. The studies of stroke events in HD patients have shown similar unfavorable prognosis. A retrospective study of 82,142 patients with ischemic stroke treated with r-tPA was performed in the United States (US) [11]. Among 1072 patients treated with r-tPA, dialysis-dependent renal failure was related to higher rates of in-hospital mortality, whereas no significant difference in ICH incidence between dialysis and non-dialysis patients was found. However, the comparison of two groups who were not given r-tPA showed the same rate of in-hospital mortality revealed that underlying medical conditions in dialysis patients may have impacted mortality. In fact, HD patients are at a markedly higher risk for hospitalized stroke compared to non-HD patients [12], and receiving HD was an independent indicator for poor functional outcome and mortality after stroke [13].

HD and peritoneal dialysis patients have a higher prevalence of stroke, compared to patients with normal renal function [12]. A Taiwan retrospective cohort study for 74,192 HD and 5974 PD patients revealed PD as well as HD patients have higher risk of ischemic stroke even after adjusting for all potential confounders and competing risk of death and matched by propensity scores [14]. Both the dialysis modalities are considered to have increased risk of stroke due to more prevalence of cardiovascular disease (CVD) risks including hypertension, diabetes, and hyperlipidemia [15]. In addition, uremia-related risk factors that include inflammation, changes in mineral metabolism inducing atherosclerosis also play a role in developing stroke [14]. Furthermore, the glucose-based dialysate used in PD is associated with more metabolic side effects, such as hyperlipidemia and peripheral insulin resistance compared to HD patient and the general population leading to increased CVD risks [16]. Since our patient had been on

PD for 7 years long before switching to HD and angiography showed coronary artery occlusion, we consider those CVD, inflammation and metabolic disorder factors might have initiated her stroke onset.

This case presented with stroke during HD procedure at a MCA lesion. Onoyama et al. [17] reported that 64% cerebral infarction developed during or within 6 h of the previous HD, whereas Toyoda et al. found that cerebral infarction occurred more frequently during or within 30 min after HD than brain hemorrhage and was related to large-artery atherosclerosis and cardioembolism [13]. The gap between the two studies might be based on limitation of infarction detection. The stroke study by Onoyama et al. was diagnosed clinically with aid of CT which is lacking high sensitivity to infarction in acute phase. The sample numbers are different between the two studies (range 16–102). Further studies are required to clarify the discrepancies.

Currently, results differ among studies, and no consensus has been established regarding administration of r-tPA in HD patients. To our knowledge, studies on r-tPA given to patients undergoing HD are lacking. In particular, we found no reports on patients who had a stroke during a maintenance HD session and were treated successfully with r-tPA. Although we achieved re-opening without complications, the number of HD patients treated with r-tPA is still small, and further investigations are needed. To this point, there is no good method to access criteria for initiation of thrombolytic therapy in HD patient. However, results from previous study showed initiation based on aPTT and other criteria not associated with increase in ICH, suggesting r-tPA therapy could be considered with patients with no contraindication on the current guideline. This case suggests that thrombolytic treatment with r-tPA, even in patients with a stroke event during HD, is effective, and highlights the importance of creating a system enabling immediate transportation of such patients to facilities for r-tPA therapy.

Compliance with ethical standards

Conflict of interest Potential financial conflicts of interest; Honoraria: Yasuhiro Hasegawa (Pfizer, Bayer, Bristol-Myers Squibb). The other authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient included in this article.

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