Repeated intravenous thrombolytic therapy with rt-PA alteplase in treatment of early recurrent ischemic stroke

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Abstract:

The 2019 year guidelines (American Heart Association / American Stroke Association – AHA/ASA) do not recommend treating recurrent acute ischemic stroke with alteplase in patients who had previous stroke in last 3 months (1,9). According to the European Stroke Organisation`s (ESO) guidelines (year 2021), there is no clear consensus. The risk of reocclusion occurs in 14-34% of patients in whom recanalisation with alteplase has been achieved (1). In this paper we present the case of our 70-year old patient with early stroke recurrence and repeated thrombolytic therapy 9 hours after the first dose of alteplase.

Keywords:

repeated thrombolytic therapy, early recurrent ischemic stroke, intravenous thrombolysis, recombinant tissue plasminogen activator, rt-PA, alteplase

Sažetak:

Ponovljena intravenozna trombolitička terapija rt-PA alteplazom u liječenju ranog recidiva moždanog udara

AHA-AHS smjernice iz 2019. godine ne preporučuju liječenje akutnog ishemijskog moždanog udara alteplazom u bolesnika koji su imali ishemijski moždani udar unatrag 3 mjeseca (1,9). Prema ESO smjernicama (2021. god.), nema jasnog konsenzusa. Rizik reokluzije se događa u 14-34% bolesnika u kojih je postignuta rekanalizacija intravenskom primjenom alteplaze (1). U ovom radu predstavljamo našeg 70-godišnjeg bolesnika s ranim recidivom ishemijskog moždanog udara te ponovljenom intravenskom trombolitičkom terapijom provedenom 9 sati nakon završetka inicijalne doze alteplaze.

Ključne riječi:

ponovljena trombolitička terapija, rani recidiv moždanog udara, intravenska tromboliza, rekombinantni tkivni plazminogen aktivator, rt-PA, alteplaza

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Introduction

The 2019 year guidelines (AHA/ASA) do not recommend treating recurrent acute ischemic stroke with alteplase in patients who had previous stroke in last 3 months (1,9). According to the European Stroke Organisation`s (ESO) guidelines (year 2021), there is no clear consensus. According to studies, the risk of poor clinical outcome (mRS-modified Rankin Scale 3-6) was not significantly increased in these patients. Recent observational studies have not shown association of previous ischemic stroke with increased risk of intracerebral bleeding. Meta-analyses that included 52 631 patients who were treated with intravenous alteplase found no evidence of increased risk for intracerebral bleeding, death or poor functional outcome in 1.7% of patients who suffered an ischemic stroke within 3 months (1). Disadvantage of these observational studies is that they included relatively small number of patients and many studies did not report in what time period stroke recurrence occurred. Therefore it cannot be concluded in what time interval thrombolytic therapy was readministered. According to the consensus of experts, it is recommended to conduct intravenous thrombolytic therapy with alteplase in individual patients who previously had minor stroke or good clinical recovery. The risk of reocclusion occurs in 14-34% of patients in whom recanalisation with alteplase has been achieved (1). In this paper we present case of our 70-year old patient with early ischemic stroke recurrence in whom thrombolytic therapy was readministered 9 hours after initial dose of alteplase.

Case presentation

70-year old patient was admitted in primary stroke center after waking up in the night with moderately severe right arm paresis and severe paresis of his right leg (NIHSS – National Institute of Health Stroke Scale 6). He was last seen well 2 hours and 50 minutes earlier. Except arterial hypertension, the patient did not have other comorbidities (mRS 0). Emergency Multislice Computed Tomography (MSCT) of brain showed no acute lesions (Figure 1). MSCT angiography showed spasm and probable thrombus of M2 segment of the left middle cerebral artery (ACM) with suspect aneurysms up to 7 mm in M1 segment of the right ACM. The patient was transfered to the Sestre Milosrdnice University Hospital Center due to mechanical thrombectomy. During the transfer (1 hour and 40 minutes after the beginning of stroke symptoms and within the therapeutic interval of 4.5 hours, intravenous alteplase was administered. Our patient recovered to the level of moderate hemiparesis of the right extremities (NIHSS 4). Digital Subtractional Angiography was performed (Figure 2) and didn't find large vessel occlusion (LVO) or aneurysm. Eleven hours after initial neurological symptoms there was again worsening of neurological deficit in terms of right sided hemiplegia (NIHSS 9) without epileptic manifestations. Emergency DSA of the brain was performed again which again excluded LVO. Control brain MSCT scan (Figure 3) and

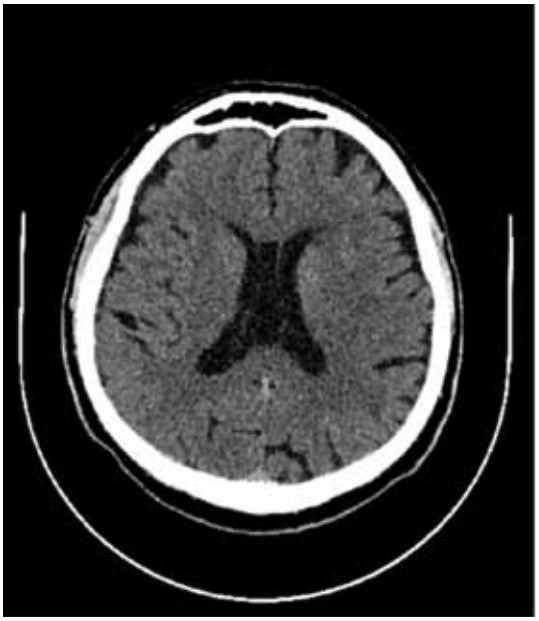

Figure 1: Brain CT before first thrombolysis

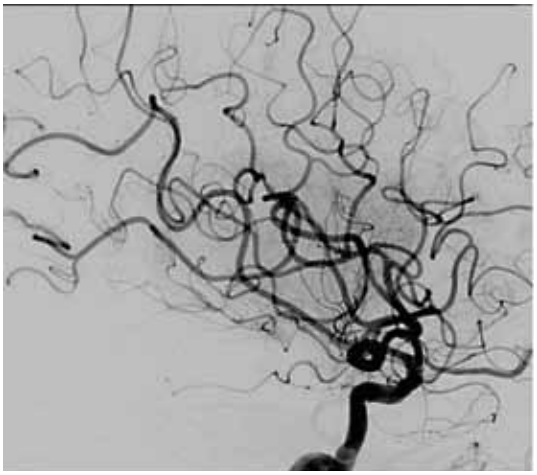

Figure 2: DSA

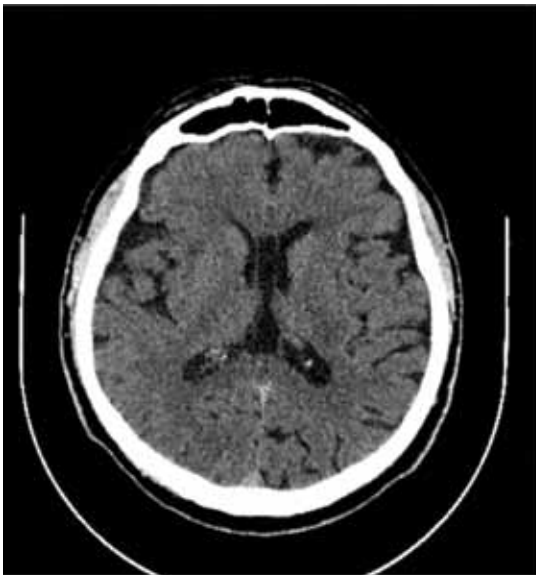

Figure 3: Brain CT after worsening

MSCT perfusion (Figure 4) showed no signs of acute ischemia with good perfusion and we have decided to readminister intravenous thrombolytic therapy (with 90 mg maximum dose of alteplase) 9 hours after the end of the first dose of rt-PA. After repeated therapy there was again clinical improvement of motor deficit to the level of mild right-sided hemiparesis (NIHSS 3). Magnetic Resonance Imaging (MRI) of brain showed a zone of fresh ischemia about 1.5 cm in diameter along the left lateral cerebral chamber and the back of the nucleus caudatus (Figures 5, 6).

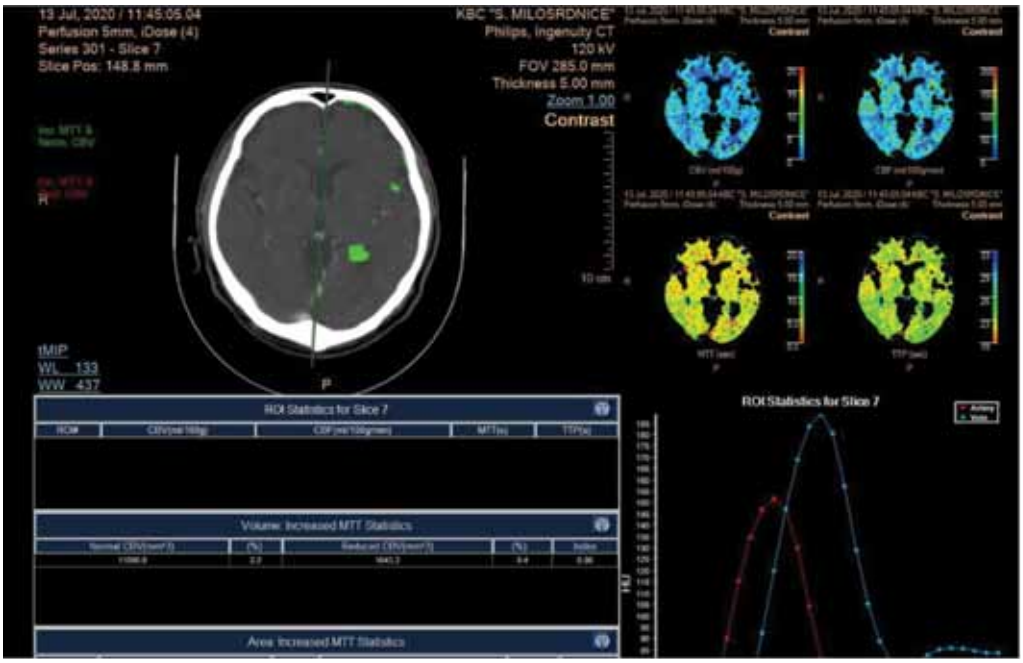

Figure 4: CT brain perfusion

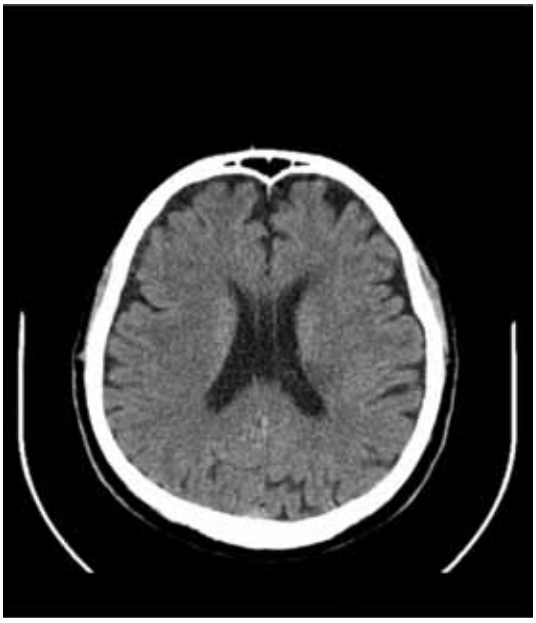

Figure 5: Control brain CT after repeated thrombolysis

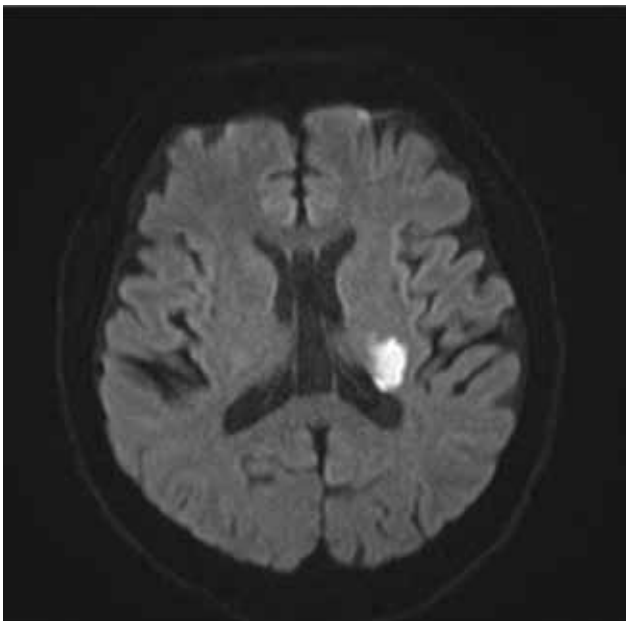

Figure 6: Brain MR after repeated thrombolysis (T2)

The early postprocedural phase was complicated with macrohematuria on the first day of hospitalization. It was stopped by rinsing the bladder, without significant decrease in red blood count. Second day of hospitalization was complicated with aggravation of inguinal hematoma at the puncture site for DSA along with swelling of the right leg and elevated D-dimers. Collor Doppler (CD) ultrasound of leg veins verified deep vein thrombosis (DVT) of the right joint femoral vein. In consultation with cardiologist, low molecular heparin was prescribed in therapeutic dose for 14 days, after which non vitamin K oral anticoagulant (NOAC) medication (rivaroxaban) was introduced. The control CD ultrasound of the leg veins showed signs of initial thrombus recanalisation, but MSCT angiography verified pseudoaneurysm of the right joint femoral artery. On 17th day of hospitalization a resection of pseudoaneurysm was performed by vascular surgeon. Days of hospitalization were additionally prolonged because of infection on the site of puncture and the need for antimicrobial therapy and active surgical treatment. Ultrasound examination of head and neck blood vessels found no significant stenosis. Holter ECG recorded no pathological rhytm. At discharge from hospital, our patient had mild right-sided hemiparesis (NIHSS 3, mRS 3-4) and neurorehabilitation was recomended.

Subsequently repeated Holter ECG recorded paroxysmal atrial fibrillation. That confirmed assumed cardioembolic etiology of a ischemic stroke and permanent anticoagulant therapy (NOAC) was continued. On following neurological controls our patient had slightly impaired fine motor skills of the right hand but he was mobile and without other neurological deficits (NIHSS 1, mRS 0).

Discussion

In this paper we have presented a patient to whom we repeated intravenous thrombolytic therapy 9 hours after the end of initial dose of rt-PA. Because of new severe neurological deficit and after the exclusion of LVO repeated rt-PA therapy was considered as the only modality of active reperfusion treatment. Readministration of intravenous alteplase after nine hours of initial dose caused no neurological deterioration. The only side effect of alteplase readministration was transitional urethrorhagia, inguinal hematoma and pseudoaneurysm as a complication of DSA and DVT. Patient was discharged from hospital with significant improvement in neurological status (NIHSS 3).

Alteplase is a thrombolytic agent that is produced by recombinant DNA technology and it was approved by United States Food and Drug Administration in 1987. Therapeutic indications are acute ischemic stroke (dose 0.9 mg/kg total to 90mg within an hour), myocardial infarction, pulmonary embolism (total doses up to 100 mg in 2-3 hours) and urological indications (3). Alteplase converts plasminogen into the proteolytic enzyme plasmin that leads to fibrinolysis and thrombus dissolution. The intravenous alteplase is metabolized through the liver with an initial half-life of 5 minutes. More than 80% of alteplase is eliminated by urine within the next 18 hours after administration (3, 4).

Repeated thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rt-PA) in cases of myocardial infarction and pulmonary embolism have been shown to be safe. There are generally few patients with repeated thrombolytic therapies in acute ischemic stroke, mainly because of fear of intracerebral haemorrhage due to the damaged blood-brain barrier, existing criteria for thrombolytic therapies (1, 2, 5) and the risk of anaphylactoid reactions in repeated administration of the drug (5). Independent risk factors for hemorrhagic transformation of cerebral infarction are age, size of the infarcted region, and diabetes mellitus (12).

Topakian et al. (20) in 2005. reported first patient who succesfully received repeated intravenous rt-PA therapy for acute ischemic stroke after four days. Smadja et al. (13) reported a case of 74-year old patient with occlusion of a basilar artery. Four hours after symptom onset conventional intravenous thrombolysis (IVT) was started. After neurological deterioration (patient became unresponsive with bilateral decerebration rigiditiy), brain MRI excluded brain haemorrhage and showed progression of thrombus. Patient was given an intravenous (IV) bolus of tenecteplase 3 hours after previous rt-PA with significant improvement in neurological status after 1 hour. Han Soo Yo et al. repeated intravenous thrombolysis on 7 out of 437 patients in period from 6 days to 76 months after initial dose, with no complications and good overall outcome in 5 patient. Alhazzaa et al. (16) analyzed all thrombolysis in period from 2008. to 2012. from Ottawa Hospital, where 3 patients had repeated intravenous thrombolysis (after 6 and 70 days of initial rt-PA). 3 patients developed petechial hemorrhage within the area of subacute infarction, but all were asymptomatic with no neurological deterioration. Kahles et al. conducted a study in Germany, Switzerland and Finland on a sample of 7537 patients. There were 19 patients who received repeated intravenous thrombolysis. The median age of these patients was 68±12 years, 37% were women, the median interval between thrombolysis was 30 days (minimum 13, maximum 50 days). Clinical improvement was achieved in 79% of patients and there were no intracranial bleeding. They concluded that patients with small areas of infarct after the initial stroke (medium size about 1.5 cm^3) can be considered for repeated thrombolytic therapy within 3 months (17). Capellari et al. (18) retrospectively reviewed the medical records of stroke patients who repeated intravenous infusion of alteplase after recurrent stroke from among the 615 consecutive stroke patients admitted to Stroke Unit Verona General Hospital, from December 2004 to September 2013. In 27 patients repeated iv thrombolytic treatment was administered once after recurrent stroke and in 3 patients twice. IV thrombolytic procedures were repeated from second day

after the initial dose to 5 years after first IV thrombolysis. They concluded that re-thrombolysis may be safe and effective when recurrent stroke occurs after a period of complete neurologic regression lasting at least 24 hours or minor disability (mRS score ≤2) lasting at least 3 months since the previous stroke. Šupe et al. (8) presented 53-year old patient with occlusion and reocclusion of basilar artery where re-thrombolytic therapy was administered after 54 hours followed by repeated mechanical thrombectomy. Sposato et al. (19) presented a 76-year old woman with known paroxysmal atrial fibrillation who was admitted because of an acute right middle cerebral artery ischemic stroke and who underwent repeated systemic thrombolysis within 110 hours. A hemorrhagic transformation of the left middle cerebral artery infarction was noted on follow-up cranial MSCT scans. The patient did not recover from the second cerebrovascular event and died 25 days after admission.

Time for repeated thrombolytic therapy from available studies varies from 48 hours to several years, but there is no significant number of intracerebral bleeding or allergic reactions (5, 6, 7, 8, 10, 11). Less satisfactory recovery was observed after the second dose of thrombolytic therapy than after the initial dose, probably as a result of previous lesion of cerebral parenchyma.

Conclusion

In summary, there is no clear expert consensus for repeated intravenous thrombolytic therapy with alteplase in patients with early cerebral infarction recurrence. From the available literature, at the time of writing this case, we found only one case report where intravenous thrombolytic therapy was repeated after 3 hours in patient with basilar artery occlusion after the initial dose of intravenous rt-PA tenecteplase was administered (13). We presented a case of our 70-year old patient with early ischemic stroke recurrence in whom thrombolytic therapy was readministered 9 hours after initial dose of alteplase with a good clinical outcome. This review speaks in favor of the safety and efficacy of administration of repeated intravenous thrombolytic therapy in thoroughly selected early ischemic stroke recurrence patients and the need for possible further reevaluation of excluding criteria in treatment of acute ischemic stroke with alteplase. The main predictor of intracerebral bleeding could be a severity of the initial neurological deficit and previous neurological damage. Further clinical trials and patient registers are needed.

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Abbreviatons:

AHA / ASA – American Heart Association / American Stroke Associtation
ESO – European Stroke Organisation
mRS – modified Rankin Scale
NIHSS – National Institute of Health Stroke Scale
MSCT – Multislice Computed Tomography
ACM – middle cerebral artery
IVT – intravenous thrombolysis
IV - intravenous
DSA – Digital Subtraction Angiography
LVO – large vessel occlusion
MRI – Magnetic resonance imaging
CD ultrasound– Color Doppler ultrasound
DVT – Deep Vein Thrombosis
NOAC – non vitamin K oral anticoagulant
rt-PA – recombinant tissue- plasminogen activator
FDA – Food and Drug Administration