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CASE REPORT

The safety and efficacy of intravenous thrombolysis for ischemic stroke in an elderly patient with thrombocytopenia

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ABSTRACT

Background: Strokes remain as one of the diseases with high mortality and morbidity, which can be prevented through prompt and concise treatment. Intravenous thrombolysis (IV-rTPA) is the mainstay treatment for hyperacute ischemic stroke with onsets of less than 4.5 hours. However, it has several contraindications that should be monitored, one of them being thrombocytopenia. **Objectives:** This case report details the use of IV-rTPA in a geriatric patient with thrombocytopenia to highlight its efficacy and safety. **Case:** An 85-year-old woman was admitted to the emergency ward with weakness in the left extremities, slurred speech, and upward-right gaze one hour prior to ER admission. She had a significant history of hypertension and type II diabetes mellitus. A physical examination revealed a muscle strength of +5/+1, palsy in the left 7th and 12th cranial nerves, an NIHSS score of 15, and a RACE score of 7. The laboratory result was positive for thrombocytopenia (96,000/µl). IV-rTPA was administered, and two hours later, the patient's NIHSS score raised to 11. During the IV-RTPA administration, there was minor gum bleeding, which was considered insignificant. The patient was admitted to the ICU and observed for the next 72 hours. No signs of bleeding or clinical deterioration were observed during that period. Numerous studies have confirmed IV-rTPA's efficacy in acute ischemic stroke treatment if administered before 4.5 hours of onset. Thrombocytopenia is known as a contraindication of IV-rTPA, which may increase the risk of bleeding. In this case, IV-rTPA was administered due to hyperacute onset and no known history of bleeding despite low platelet count. **Conclusion:** IV-rTPA may be considered if the benefits outweigh the risks, coupled with thorough monitoring of the patient's condition.

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Highlights

1. Stroke is one of the top causes of death anddisability in the world.
2. Thrombocytopenia is a condition that poses the risk of bleeding in patients, so administering rtPA in ischemic stroke patients is needed.

BACKGROUND

Stroke is one of the top causes of death anddisability in the world (Krishnamurthi et al., 2020). Due to high medical costsand resulting serious disability, this disease is still an unresolved global problem. In 2010, according todata from the American Stroke Association (ASA), stroke treatment costs reached $73 billion and rehabilitation costs reached $10 billion (Godwin et al., 2011). In addition, it is estimated that 32,000 neuron cells are damaged per second due to stroke (Saver, 2006).

Human brain cells can be damaged quickly and irreversibly over time, meaning therapy must be administered immediately (Saver, 2006). Based on the American Heart Association (AHA)/ASA guideline that was updated in 2019, there are several therapeutic options for acute stroke treatment. Patients with stroke symptoms with an onset of fewer than 4.5 hours may be considered for intravenous administration of recombinant tissue plasminogenactivator (rTPA) with either alteplase ortenecteplase. Apart from administering rTPA, thrombectomies are also a therapeutic option foracute stroke patients with onsets below 24 hours in certain cases. Prompt and appropriate treatment is expected to reduce disability and death from stroke in the future. The use of rTPA, such as intravenous alteplase, as initial therapy in ischemic stroke, is widely recognized. The 2019 AHA/ASA guideline listed intravenous alteplase as an acute ischemic stroke treatment with primary recommendation (class I, recommendation level A) by meeting certain criteria for alteplase use (Powers et al., 2019).

One of the contraindications for administering rtPA in ischemic stroke patients is thrombocytopenia of under 100,000/mm^3 because this condition poses the risk of bleeding in patients (class III) (Powers et al., 2019). However, the risk-benefit ratio must be carefully considered in each case, bearing in mind that bleeding incidence in alteplaseadministration is very rare, especially in patients with no history of spontaneous bleeding (Fugate and Rabinstein, 2015).This is also supported by the inconsistency of data obtained from several previous studies (Brunner et al., 2011; Frank et al., 2013; Gensicke et al., 2018; Meretoja et al., 2010; Mowla et al., 2017).

OBJECTIVES

This case report presents a case of hyperacute ischemic stroke where rtPA therapy was administered to a geriatric patient with thrombocytopenia.

CASE

The subject is an 85-year-old woman with complaints of weakness in the left hand and leg. She was still able to communicate, but not clearly (dysarthria), and her eyes continuously glanced to the right. She had an onset of one hour after theincident when she arrived at the emergency room. The patient had a hypertension history dating back one year. She had also had type 2 diabetes mellitus for 15 years, controlled with the drugs bisoprolol 5 mg, amlodipine 10 mg, and a combination of metformin 500 mg with linagliptin 5 mg. She had no history of stroke or previous cardiac abnormalities. The patient had a history of hepatitis C treatment without cirrhosis of the liver or liver cancer. The patient was able to carry out daily activities independently and was able to walk. Prior to the incident, the patient was not physically active.

Upon physical examination, the patient had compos mentis awareness with stage II hypertension. A neurological examination on the face found dysarthria and UMN type facial palsy on the left side.There were no signs of meningeal irritation. Based on the MRC scale, muscle strength was identified in the patient's left hand and leg. The sensory examination yielded normal results. Physiological reflexes on the left side of the body appeared to be increasing, and positive Babinski reflexes were found in the left foot. The patient's NIHSS score on arrival was 15 and her RACE score was 7. The laboratory test revealed random blood sugar at 148 mg/dl, platelets at 96,000/µl, and prothrombin time of 10.3 seconds with an INR of 0.9. The other laboratory test results were normal.

From the head CT-scan without contrast **(Fig. 1**), there were no signs of infarction/ischemia or bleeding. Based on these results, the ASPECTS scorewas 10. However, in this patient, further radiological examinations such as CTA, MRI, and MRA of the head had not been carried out to determine a definite largevessel occlusion (LVO) diagnosis.

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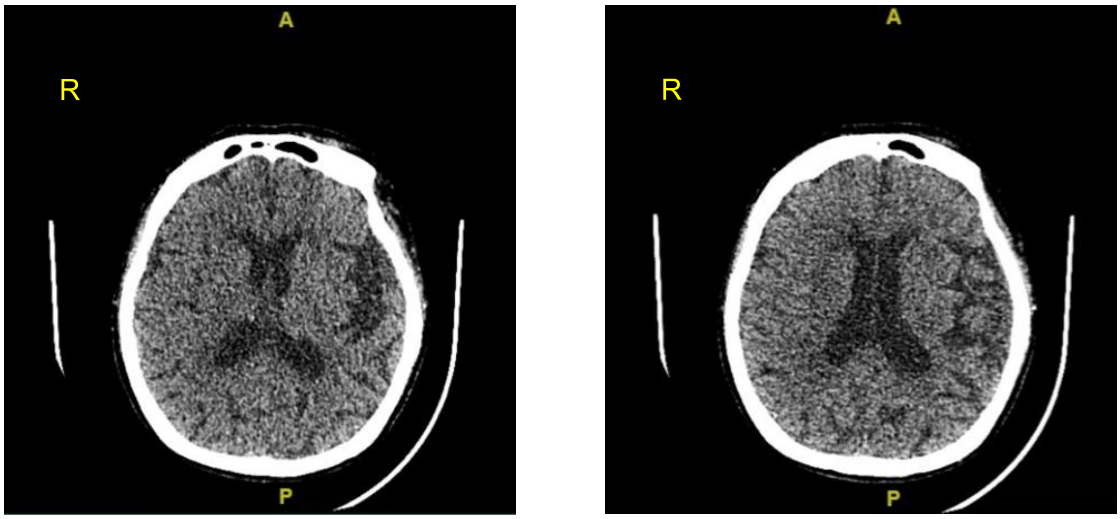
The patient was diagnosed with a hyperacute phase of ischemic stroke with controlled type 2 diabetes mellitus, stage II hypertension, and thrombocytopenia. The patient was given rTPA therapy (alteplase) with consideration of the benefits over the risks. Alteplase was administered as a bolus with 10% of the total dose (dose 0.9 mg/kg) for one minute and then slowly overone hour.

Vital signs,neurological symptom improvement, andbleeding complications were closely observed during intravenous administration. After one minute of alteplase bolus administration there was a change or there was no change and include the unit after 1 to 2, and motor changes in the left lower extremity from 1 to 2. There was also improvement in the oculomotor nerve as the patient no longer glanced to the right. Dysarthria and weakness on the face were still present.

The patient's NIHSS score went from 15 to 11. During the alteplase administration, blood streaks were found in the gums, but the amount was insignificant. The alteplase administration did not have significant results, thus, a thrombectomy was considered. However, due to the patient's age and the risk of bleeding that might occur, further care and treatment was carried out conservatively using drugs and physiotherapy.



A. Ganglionic level **B.** Supraganglionic level

Figure 1. Head CT-scan of without contrast, no hypodensity or hyperdensity was found at the ganglionic (A) and supraganglionic (B) levels.

The patient was treated in the ICU for up to 72 hours after alteplase administration. While in the ICU, the patient did not experience significant clinical improvement. However, there were no signs of bleeding or worsening of the condition. The patient was then moved to the medical ward on the third day of treatment. Next treatment was carried out conservatively using a combination of antiplatelets and anticoagulants. This included enoxaparin injections with a 0.4 mL dose twice per day for five days and oral cilostazol with a dose of 50 mg twice per day. During the recovery period, the patient underwent rehabilitation with physiotherapy using electrical stimulation (electrostimulation) as well as active and passive facial and extremity muscle exercises.

After treatment and physiotherapy, the patient's motor strength remained at a 2 in the shoulder area and lower extremities. Weakness in the face began to improve, the patient could chew food, and she spoke more clearly than before. The patient's platelet count on day 9 was 129,000/µl without any additional therapy to increase the platelet count.

When discharged from the hospital, based on clinical and physical examinations, the patient's NIHSS score improved to 9. The patient had no improvement in her left extremities' motor strength. An assessment based on the Glasgow Outcome Scale Extended (GOSE) obtained a score of 3 (lower severe disability) and an assessment based on the Modified Rankin Scale showed a score of 4. The patient was mobilized with a wheelchair. Physiotherapy is still being carried out every day for up to three months

after the stroke. Follow-ups with the patient could not be carried out because the patient did not return to the polyclinic.

DISCUSSION

Hypertension is the risk factor for stroke, with the most frequent incidence in men at young age. 64% persons with stroke was hypertensive (Wajngarten and Silva, 2019). Hypertension is defined as the elevation of blood pressure, systolic between 120-129 mmHg, and diastolic more than 80 mmHg. When diastolic blood pressure (DBP) is elevated more than 80 mmHg, the risk of stroke also elevated by 3.453-fold (Brown et al., 2022). During stroke events, the systolic blood pressure (SBP) will increase during 24-hour of stroke onset. Elderly combined with hypertension, resulting an unfavorable outcome to the patient (Weiss et al., 2016).

Type 2 diabetes (T2DM) causes alterations in vasculature (micro and macrovascular) with several complications such as stroke with the consequences of cerebral small vessel disease with unfavorable clinical outcome, including mortality (Chen et al., 2017). So, diabetes is one of independent risk factor of stroke with a higher incidence of ischemic stroke compare to hemorrhagic or lacunar infarcts, due to the coexistence of microvascular disease with hypertension (Tun et al., 2017). Hypertension and diabetes impair the protective vascular mechanism, causing ischemia. Hyperglycemia exacerbate neural damage by stimulating vascular inflammation, increasing blood–brain barrier (BBB) permeability, impairing cellular metabolism, and promoting tissue acidosis, which made the worse outcome after the stroke event (Harada et al., 2012). The mortality rate of diabetic patients with stroke was 2-fold higher, even after receiving thrombolytic therapy. The morbidity in the form of intracerebral hemorrhage increase by 2.26-fold when administered intravenously, and 4.2-fold when administer intra-arterially (Martini and Kent, 2007).

Stroke pattern in diabetic patients also associated with high risk of subsequent stroke, functional disability, long hospital stays, mortality and development of dementia (Tun et al., 2017). Hyperglycemia increase oxidative stress and lead several pathological processes due to high production of reactive oxygen species (ROS). ROS inhibits glyceraldehyde 3-phosphate dehydrogenase (GADPH) in glycolysis, which also alters 5 signaling pathways (polyol pathway flux; (2) increased formation of advanced glycation end products (AGEs); (3) increased expression of receptors for AGEs; (4) activation of protein kinase C isoforms; and (5) overactivity of hexosamine pathway) that contribute to endothelial dysfunction and accelerate atherosclerosis (Tun et al., 2017).

Acute hypertensive response was detected in this patient post stroke onset, represent as stage II hypertension. Acute hypertensive response is an elevation of blood pressure (BP $\geq$ 140/90 mmHg) during 24-hour after the onset of stroke sign and return to normal within few days, is common in 60% patients with stroke. For medical management, antihypertensive agent administration is needed to reduce the blood pressure to normal range (Qureshi, 2008). Acute hypertensive response monitoring during 24-hour after the onset is important to predict the outcome in elderly (Weiss et al., 2016).

Thrombosis in the form of thrombocytopenia (platelet blood count less than 150 K/µL) in older patients after stroke event increase the Charlson comorbidity index, but not increase the mortality risk during hospitality period (Wang et al., 2023). However a study has been pointed out the importance of platelet count during the stroke management. Patients with 249–450 $\times 10^9$ /L platelet count had 1.21-fold higher recurrent stroke, with 1.43-fold higher mortality (Yang et al., 2019). Other stated that mean platelet volume (MPV) and platelet distribution width had been used as biomarker of platelet function and activation. High MPV associated with thromboembolism, myocardial infarction and stroke, while larger PDW indicated pro-thrombotic (Sharma and Goyal, 2020).

Antiplatelet agent is needed for reducing the risk of subsequent risk (Strozyk and Ocava, 2008). The rTPA administration in this case was considered quite safe while still considering the benefits and risks to the patient after administration. Alteplase is quite effective for clinical improvement, as has been reported in several previous studies (Chen et al., 2022; Micieli et al., 2009). The usage of alteplase as the first step therapy of intravenous thrombolysis treatment for ischemic stroke for more than 10 years can stimulate recanalization of occluded vessels (Micieli et al., 2009). The usage of alteplase for elderly to improve the clinical sign (discharge modified Rankin Scale (mRS), symptomatic

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intracerebral haemorrhage (sICH) and NIHSS) was comparable with the younger patients, although the post discharge mortality was higher in elderly (>80 years old), 9% vs. 6% (Huang et al., 2021). However, a study conducted at 216 patients with stroke showed low improvement after 24-hour of alteplase administration, with the mortality rate after 3-months was 20.2%. for survivors, 44% (75 patients) had poor outcome (Saposnik et al., 2004).

Strengths and Limitations

The response of alteplase administration to clinical improvement is not the same for every patient. In geriatric patients with thrombocytopenia, it is necessary to be aware of the greater risk of bleeding compared to patients in general. For this reason, further research is needed regarding the safety profile of alteplase administration, especially in geriatric patients with thrombocytopenia.

CONCLUSION

The administration of rTPA in this case was considered safe while still considering the benefits and risks to the patient after administration.

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Conflict of Interest

All authors have no conflict of interest.

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Author Contribution

The author contributed to all processes in this study, including preparation, data gathering and analysis, drafting, and approval for the manuscript's publication.

Patient Consent for Publication

This case report has been approved by the patient and his/her guardian.

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