

Case Report,

Safety and Efficacy of Intravenous Thrombolysis for Ischemic Stroke in Elderly Patient with Thrombocytopenia

Ricky Candra Wijaya*

Emergency Department, Mitra Keluarga Kenjeran Hospital, Surabaya, Indonesia

Email Address: huangricky95@gmail.com

Abstract:

Introduction: Stroke remains as one of the diseases with a high mortality and morbidity which could be prevented by a prompt and concise treatment. Intravenous thrombolysis (IV-rTPA) is the mainstay treatment for hyperacute ischemic stroke with onset less than 4.5 hours. However, there are several contraindications that should be monitored, one of them being thrombocytopenia. We would like to report the use of IV-rTPA in geriatric patient with thrombocytopenia to highlight the efficacy and safety profile of the drug.

Case Report: A 85-year-old woman was admitted to the emergency ward with weakness on the left extremities, slurred speech, and right-upward gaze of the eyes one hour prior to the admission in ER. Her history was significant for hypertension and type II diabetes mellitus. Physical examination revealed a muscle strength of +5/+1, left 7th and 12th cranial nerves palsy, a NIHSS score of 15, and a RACE score of 7. The laboratory result was significant for thrombocytopenia (96.000/ μ l). IV-rTPA was administered and two hours later, we noticed an improvement of the patient's NIHSS score to 11. During the IV-rTPA administration, we noted a minor gum bleed, 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.

Discussion: Numerous studies have confirmed the efficacy of IV-rTPA in acute ischemic stroke 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 is administered due to hyperacute onset and no known history of bleeding, even though the platelet count was low. Therefore, IV-rTPA may be considered if the benefits outweigh the risks with a thorough monitoring of the patient's condition.

Keywords: geriatric, hyperacute is chemic stroke, intravenous thrombolysis, thrombocytopenia

Introduction:-

Stroke is one of the highest causes of death and disability in the world ^[1]. With high medical costs and resulting serious disability, this disease is still unresolved global problem. In 2010, according to data from the American Stroke Association, stroke treatment costs reached 73 billion US dollars and rehabilitation costs reached 10 billion US dollars ^[2]. In addition, an estimated 32 thousands neuron cells are damaged per second due to stroke ^[3].

The jargon of time is brain emphasizes that human brain cells can be damaged quickly and irreversibly over time, so therapy must be given

immediately. Based on the AHA/ASA guideline that was updated in 2019, there are several therapeutic options for the treatment of acute stroke. Patients with stroke symptom onset less than 4.5 hours may be considered for intravenous administration of recombinant tissue plasminogen activator (rtPA) with either Alteplase or Tenecteplase. Apart from giving rtPA, thrombectomy is also a therapeutic option for acute stroke patients less than 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 place intravenous Alteplase as the treatment of acute ischemic stroke with primary recommendation (class I, recommendation level A) by meeting certain criteria for Alteplase use.

One of the contraindications to giving rtPA in ischemic stroke patients is thrombocytopenia $< 100,000/\text{mm}^3$ because this condition has the potential to pose a risk of bleeding in patients (class III) [4]. However, we need to be wise in taking the risk-benefit ratio in each case, bearing in mind that the incidence of bleeding in Alteplase administration is very rare, especially in patients who have no history of spontaneous bleeding [11]. This is also supported by the inconsistency of data obtained from several previous studies [5-10].

Through this case report, I present a case of hyperacute ischemic stroke that administrated by rtPA therapy in a geriatric patient with thrombocytopenia.

Case report:-

An 85 year old woman with complaints of weakness of the left hand and leg, still able to communicate but not clear (dysarthria) and eyes glance to the right with an onset of 1 hour after the incident when she arrived at the emergency room. The patient had a history of hypertension for 1 year and Type 2 Diabetes Mellitus for 15 years controlled with the drugs Bisoprolol 5 mg, Amlodipine 10 mg, and the combination of Metformin 500 mg with Linagliptin 5 mg. There was no history of stroke or previous cardiac abnormalities. The patient has a history of treated hepatitis C without cirrhosis of the liver or liver cancer. Patient can carry out daily activities independently and are able to walk. Prior to the incident, the patient wasn't in physical activity.

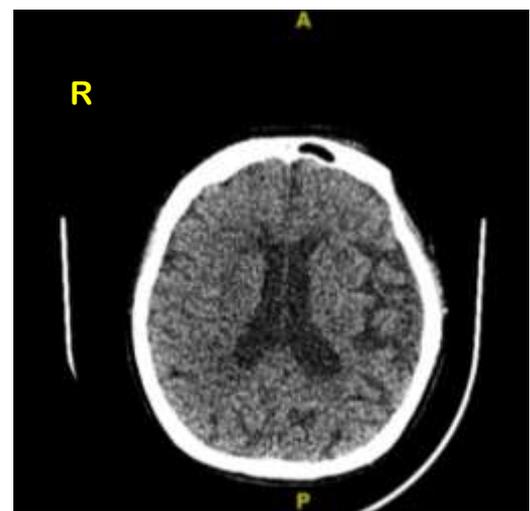
On physical examination, I found compos mentis awareness with stage II hypertension. Neurological examination on the face found dysarthria and UMN type facial palsy on left side. There were no signs of meningeal irritation. Based on the MRC scale, muscle strength was obtained 1 on the patient's left hand and leg. Sensory examination was normal. Physiological reflexes on the left side of the body seem to be increasing and positive Babinski reflex is found on the left foot. The NIHSS score at arrival was 15 and the RACE score was 7. The results of

laboratory tests were random blood sugar 148 mg/dl, platelets $96,000/\mu\text{l}$, prothrombin time 10.3 seconds with an INR of 0.9. The results of other laboratory tests were normal.

From the head CT-scan without contrast (Fig. 1) there were no signs of infarction/ischemia or bleeding. Based on these results, ASPECTS score was 10. However, in this patient, further radiological examinations such as CTA, MRI and MRA of the head hadn't been carried out to determine a definite diagnosis of LVO (Large Vessel Occlusion).



A. Ganglionic level



B. Supraganglionic level

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

The patient was diagnosed with a hyperacute phase of ischemic stroke with controlled Diabetes Mellitus type 2, stage II hypertension, and thrombocytopenia. The patient was given rtPA therapy (Alteplase) with consideration of the benefits than the risks. Alteplase is given as a bolus for 1 minute as much as 10% of the total dose (dose 0.9 mg/kg) and then given slowly over 1 hour.

During intravenous administration, vital signs, improvement of neurological symptoms and bleeding complications were closely observed. After 1 minute of Alteplase bolus administration, there was no change in the patient's symptoms. After the 1-hour dose was completed, there were motor changes in the upper left extremity in the shoulder area from 1 to 2 and motor changes in the left lower extremity from 1 to 2. There was also improvement in the oculomotor nerve so that the patient no longer glance to the right. Dysarthria and weakness on the face is still found. There was a change in the patient's NIHSS score from 15 to 11. During Alteplase administration, blood streak was found in the gums but the amount was not significant. The results of Alteplase administration in patients were less significant, so that thrombectomy was considered, but due to age and the risk of bleeding that might occur, further care and treatment was carried out conservatively using drugs and physiotherapy.

The patient were treated in the ICU for up to 72 hours after administration of Alteplase. While in the ICU, the patient's condition 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 3rd day of treatment. Next treatment was carried out conservatively using a combination of antiplatelet and anticoagulant, such as Enoxaparin injection with 0.4 mL dose twice per day for 5 days and oral Cilostazol 50 mg twice per day. During the recovery period, 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 still 2 in the shoulder area and the motor in the lower extremities still 2. Weakness in the face began to improve; the patient could chew food, and spoke more clearly than before. The results of the patient's platelet evaluation on

day 9 were 129,000/ μ l without any additional therapy to increase the platelet count.

When discharge from the hospital, based on clinical and physical examination the patient improved in NIHSS score to 9. The motor strength of the patient's left extremity was still the same. Assessment based on the Glasgow Outcome Scale Extended (GOSE) obtained a score of 3 (lower severe disability) and Modified Rankin Scale 4. The patient mobilized with a wheelchair. Physiotherapy is still being carried out every day for up to 3 months after a stroke.

Future follow up of the patient could not be carried out because the patient didn't return to the polyclinic.

Discussion:-

Alteplase is a therapeutic option and the only intravenous thrombolytic drug approved by the Food and Drug Administration (FDA) for the treatment of ischemic stroke with a recommendation level IA. Alteplase administration is time-dependent and should be given as soon as possible after a stroke is detected. Alteplase has been shown to benefit patients with acute stroke symptoms when given as soon as possible, with a maximum range of 3-4.5 hours after the onset of ischemic stroke [4, 17]. Alteplase should be administered in an intensive care unit or stroke unit. Observation is carried out by paying attention to the presence of symptoms such as headache, nausea, vomiting or worsening in the neurological examination and observing signs of bleeding. Termination of Alteplase administration can be done if these signs are found and immediately repeated the head CT-scan. Administration of Alteplase is recommended in acute ischemic stroke patients with blood pressure < 185/110 mmHg. Blood clotting factors that are considered safe and have no potential for bleeding are INR < 1.7 or PT < 15 seconds. CT-scan or MRI for evaluation 24 hours after Alteplase administration, before administration of anticoagulants or antiplatelet drugs is also recommended.

One of the contraindications to rtPA administration is thrombocytopenia. According to the AHA, a platelet count < 100,000/ mm^3 is a contraindication for giving rtPA because it can increase the possibility of intracranial bleeding [7,11]. A study from Yang et al., 2019 said that ischemic stroke patients who had

thrombocytopenia have a higher risk of bleeding stroke and worse outcomes than patients who hadn't thrombocytopenia [10]. However, the study by Mowla et al. (2017) showed that intracranial bleeding was only found in 2 of 26 cases of acute ischemic stroke with thrombocytopenia who received rtPA [13]. From several studies, it was found that the incidence of bleeding during and after administration of Alteplase was very rare. In addition, early administration of Alteplase can be performed in patients who don't have bleeding disorders or have no suspicion of platelet disorders without having to wait for laboratory results so as not to delay drug administration [12-15]. Therefore, in this case the administration of Alteplase was still carried out.

According to a study by Nogueira et al., 2009, mechanical thrombectomy in patients with impaired hemostasis didn't show a significantly increased risk of intracranial bleeding or other serious complications. Successful revascularization is associated with improved clinical condition of the patient and reduced mortality. However, the outcome was no better than that of patients with normal hemostasis.

In the management of acute stroke, Alteplase intravenous administration doesn't consider age and safe for patients with the onset of ischemic stroke symptoms less than 4.5 hours [4]. Research by Bluhmki et al., 2020 also showed good results in patients aged > 80 years who were given Alteplase according to applicable standard criteria [16]. Age is not the only consideration when administering Alteplase. Giving Alteplase to patients aged > 80 years can be considered the benefits and risks according to the patient's condition.

In this case, administration of intravenous rtPA was considered on the basis of the presence of characteristic symptoms with onset of attack less than 4.5 hours and no signs of bleeding or infarction on non-contrast head CT-scan, even though the patient had thrombocytopenia (96,000/ μ l). Alteplase administration is continued with close observation for signs of bleeding. Early administration of Alteplase is carried out without waiting for laboratory results in the hope that the benefits obtained will be greater than the losses incurred if the administration is delayed.

rtPA is still performed in ischemic stroke patients, even with suspicion of large vessel occlusion, if the onset of stroke is less than 4.5 hours.

However, there was no significant difference in outcome after mechanical thrombectomy between groups of patients who administrated and didn't administrated rtPA [18]. In this case rtPA didn't provide clinical improvement because it was suspected that there was a blockage in the large vessels with a RACE score above 5. The 2019 AHA/ASA guideline recommend mechanical thrombectomy in stroke patients who meet the following criteria, including (1) pre-stroke inpatient score 0-1 (2) presence of occlusion of the internal carotid artery or anterior branch of M1-MCA (3) age > 18 years (4) NIHSS score > 6 (5) ASPECTS > 6. Mechanical thrombectomy was not performed in this case because consider the patient's age and the presence of thrombocytopenia.

Conclusion:-

The administration of rtPA 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, but the response to clinical improvement is not the same for each patient. In geriatric patients and 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.

References:-

- [1] Krishnamurthi, R., Ikeda, T. and Feigin, V., 2020. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology*, 54(Suppl. 2), pp.171-179.
- [2] Godwin, K., Wasserman, J. and Ostwald, S., 2011. Cost Associated with Stroke: Outpatient Rehabilitative Services and Medication. *Topics in Stroke Rehabilitation*, 18(sup1), pp.676-684.
- [3] Saver, J., 2006. Time Is Brain—Quantified. *Stroke*, 37(1), pp.263-266.

- [4] Powers, W., Rabinstein, A., Ackerson, T., Adeoye, O., Bambakidis, N., Becker, K., Biller, J., Brown, M., Demaerschalk, B., Hoh, B., Jauch, E., Kidwell, C., Leslie-Mazwi, T., Ovbiagele, B., Scott, P., Sheth, K., Southerland, A., Summers, D. and Tirschwell, D., 2019. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, 50(12).
- [5] Brunner, F., Tomandl, B., Schröter, A., Mellinghoff, C., Haldenwanger, A., Hildebrandt, H. and Kastrup, A., 2011. Hemorrhagic complications after systemic thrombolysis in acute stroke patients with abnormal baseline coagulation. *European Journal of Neurology*, 18(12), pp.1407-1411.
- [6] Gensicke, H., Al Sultan, A., Strbian, D., Hametner, C., Zinkstok, S., Moulin, S., Bill, O., Zini, A., Padjen, V., Kägi, G., Pezzini, A., Seiffge, D., Traenka, C., Rätty, S., Amiri, H., Zonneveld, T., Lachenmeier, R., Polymeris, A., Roos, Y., Gumbinger, C., Jovanovic, D., Curtze, S., Sibolt, G., Vandelli, L., Ringleb, P., Leys, D., Cordonnier, C., Michel, P., Lyrer, P., Peters, N., Tatlisumak, T., Nederkoorn, P. and Engelter, S., 2018. Intravenous thrombolysis and platelet count. *Neurology*, 90(8), pp.e690-e697.
- [7] Mowla, A., Kamal, H., Lail, N., Vaughn, C., Shirani, P., Mehla, S., Rajabzadeh-Oghaz, H., Deline, C., Ching, M., Crumlish, A. and Sawyer, R., 2017. Intravenous Thrombolysis for Acute Ischemic Stroke in Patients with Thrombocytopenia. *Journal of Stroke and Cerebrovascular Diseases*, 26(7), pp.1414-1418.
- [8] Meretoja, A., Putaala, J., Tatlisumak, T., Atula, S., Artto, V., Curtze, S., Häppölä, O., Lindsberg, P., Mustanoja, S., Piironen, K., Pitkäniemi, J., Rantanen, K., Sairanen, T., Salonen, O., Silvennoinen, H., Soine, L., Strbian, D., Tiainen, M. and Kaste, M., 2010. Off-Label Thrombolysis Is Not Associated With Poor Outcome in Patients With Stroke. *Stroke*, 41(7), pp.1450-1458.
- [9] Frank, B., Grotta, J., Alexandrov, A., Bluhmki, E., Lyden, P., Meretoja, A., Mishra, N., Shuaib, A., Wahlgren, N., Weimar, C. and Lees, K., 2013. Thrombolysis in Stroke Despite Contraindications or Warnings?. *Stroke*, 44(3), pp.727-733.
- [10] Yang, Y., Liu, B., Wu, L., Guan, X., Luo, Y., Jiang, C., Gupta, S., Huang, Z. and Everett, G., 2019. Safety of Intravenous Thrombolysis for Acute Ischemic Stroke in Patients with Thrombocytopenia. *Cerebrovascular Diseases*, 48(3-6), pp.157-164.
- [11] Fugate, J. and Rabinstein, A., 2015. Absolute and Relative Contraindications to IV rt-PA for Acute Ischemic Stroke. *The Neurohospitalist*, 5(3), pp.110-121.
- [12] Cucchiara, B., Jackson, B., Weiner, M. and Messe, S., 2007. Usefulness of Checking Platelet Count Before Thrombolysis in Acute Ischemic Stroke. *Stroke*, 38(5), pp.1639-1640.
- [13] Mowla, A., Kamal, H., Lail, N., Vaughn, C., Shirani, P., Mehla, S., Rajabzadeh-Oghaz, H., Deline, C., Ching, M., Crumlish, A. and Sawyer, R., 2017. Intravenous Thrombolysis for Acute Ischemic Stroke in Patients with Thrombocytopenia. *Journal of Stroke and Cerebrovascular Diseases*, 26(7), pp.1414-1418.
- [14] Breuer, L., Huttner, H., Kiphuth, I., Ringwald, J., Hilz, M., Schwab, S. and Köhrmann, M., 2013. Waiting for Platelet Counts Causes Unsubstantiated Delay of Thrombolysis Therapy. *European Neurology*, 69(5), pp.317-320.
- [15] Demaerschalk, B., Kleindorfer, D., Adeoye, O., Demchuk, A., Fugate, J., Grotta, J., Khalessi, A., Levy, E., Palesch, Y., Prabhakaran, S., Saposnik, G., Saver, J. and Smith, E., 2016. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke. *Stroke*, 47(2), pp.581-641.
- [16] Bluhmki, E., Danays, T., Biegert, G., Hacke, W. and Lees, K., 2020. Alteplase for Acute Ischemic Stroke in Patients Aged >80 Years. *Stroke*, 51(8), pp.2322-2331.
- [17] Zitek, T., Ataya, R., Brea, i., 2020. Using Tenecteplase for Acute Ischemic Stroke: What Is the Hold Up. 21(2): 199–202.
- [18] Suzuki, K., Matsumaru, Y., Takeuchi, M., Morimoto, M., Kanazawa, R., Takayama, Y., Kamiya, Y., Shigeta, K., Okubo, S.,

Hayakawa, M., Ishii, N., Koguchi, Y., Takigawa, T., Inoue, M., Naito, H., Ota, T., Hirano, T., Kato, N., Ueda, T., Iguchi, Y., Akaji, K., Tsuruta, W., Miki, K., Fujimoto, S., Higashida, T., Iwasaki, M., Aoki, J., Nishiyama, Y., Otsuka, T. and Kimura, K., 2021. Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome among Patients with Acute Ischemic Stroke. *JAMA*, 325(3), p.244.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>.