Original Article

Althea Medical Journal
ISSN Online: 2337-4330
https://doi.org/10.15850/amj.v11n4.3364

Recombinant Tissue Plasminogen Activator Affects Extremity Motor Progress in Acute Ischemic Stroke Patients

Dhianty Ramadhani,[1] Nuri Amalia,[2] Mirasari Putri[3]

[1]Faculty of Medicine, Universitas Islam Bandung, Indonesia
[2]Department of Neurology, Faculty of Medicine, Universitas Islam Bandung, Indonesia
[3]Department of Biochemistry, Nutrition and Biomolecular, Faculty of Medicine, Universitas Islam Bandung, Indonesia

Abstract

Background: Decreased motor function is the most common disorder caused by stroke, leading to disability. Early recanalization is the potential therapy for acute ischemic stroke, by using recombinant tissue plasminogen activator (rtPA). This study aimed to analyze the effectiveness of rtPA therapy on the motor progression of extremities in acute ischemic stroke patients.

Methods: This was a retrospective cohort study using secondary data from medical records of 45 patients with acute ischemic stroke who received rtPA therapy in Al Islam Bandung Hospital, Indonesia in 2022. The limb motor progress was designated as an increase in strength motoric function skills of the left and right arms, as well as the left and right legs which were influenced by the neuroplasticity process. Marginal homogeneity test was used with significance at $p<0.05$.

Results: Therapy of rtPA improved affected limb motor progress in patients ($p=0.000$). Before the administration of rtPA, all patients experienced muscle weakness. After 24 hours of rtPA therapy, patients experienced a decrease in muscle strength (9.5%), a steady state (28.6%), and increased in muscle strength (61.9%). After 72 hours, it was found that patients experienced a decrease in muscle strength (9.5%), a steady state (16.7%), and increased in muscle strength (76.2%).

Conclusion: Administration of rtPA significantly affects the progress of limb motor improvement in acute ischemic stroke patients. This study supports rtPA as a primary therapeutic option for acute ischemic stroke patients and is expected to contribute to improving the management and recovery of stroke, a critical illness associated with aging.

Keywords: Acute ischemic stroke, motor progress, rtPA

Althea Medical Journal.
2024;11(4):229–234

Received: July 20, 2023
Accepted: October 18, 2024
Published: December 30, 2024

Correspondence:
Mirasari Putri
Department of Biochemistry, Nutrition and Biomolecular, Faculty of Medicine, Universitas Islam Bandung, Indonesia,
Jl. Taman Sari No 22, Bandung, Indonesia

E-mail:
mirasari.putri@unisba.ac.id

Introduction

The World Health Organization ranks stroke as the second major cause of mortality and the third largest cause of disability worldwide.[1,2] About 33.3% of stroke cases occur in the age group of 55–64 years old, and about 87% are ischemic strokes.[3,4] Ischemic stroke can be caused by the blockage of blood vessels supplying the brain. Reducing blood supply to the brain affects the energy consumption process of nerve tissues. When ischemic stroke has affected the centre of motor coordination, it can cause a decreased mobility in patients.[5] Decreased motor function is the most common disorder caused by stroke.[6,7] Stroke can result in persistent disability, which can impair the work capability.[3] Surviving patients may recover without disability or develop mild, moderate, or severe disability. To reduce complications, healthcare professionals must provide adequate follow-up and therapeutic assistance to patients in restoring their health and function and to prevent further disability.[6]

Current therapy for ischemic stroke aims to enhance patients' long-term results. Early recanalization is currently the promising treatment for acute ischemic stroke.[8] The

recombinant tissue plasminogen activators (rtPA) used in IV therapy are a class of thrombolytic drugs that can reduce blood clots in blocked blood vessels in parts of the brain, thereby increasing oxygen supply and blood flow in the motoric area.[9] Thus, giving the rtPA can cause recanalization at the location of lesion of the motor cortex and/or pyramidal tract. Lesions of the motor cortex and/or pyramidal tract cause adaptive changes in the surrounding cortical areas with the formation of new neural tissue. This neural plasticity process is involved in the recovery of motor function lost after a stroke.[10] Nevertheless, this therapeutic approach is rarely practiced in Indonesia.

In Indonesia, the management approach focuses on addressing tissue damage resulting from thromboembolism. In contrast, developed countries therapeutic strategies focuses on revascularization to prevent brain tissue damage.[11] This caused by limited research on determining the effect of rtPA therapy on limb motor progress in acute ischemic stroke patients. Thus, this study aimed to analyze the effectiveness of rtPA therapy against the motor progression of extremities in acute ischemic stroke patients.

Methods

This research was an analytic observational study with a retrospective cohort design conducted in 2022 using medical records of acute ischemic stroke patients treated at the Al-Islam Bandung Hospital, Indonesia in 2019–2021 and given rtPA therapy. According to the criteria of the 2021 National Guidelines of Medical Services for Stroke Management, Al Islam Bandung Hospital was included in the Acute Stroke Ready Hospital (ASRH) category, due to its capability to perform intravenous thrombolysis. In addition, Al Islam Bandung Hospital was a secondary-level hospital, one of the referral hospitals for stroke patients in Bandung, West Java, Indonesia.

This study used non-probability sampling with a total sampling method to determine the sample selection. Incomplete medical records, deceased patients, and patient who did not complete treatment were excluded.

The independent variable of this study was the effectiveness of rtPA, while the dependent variable was the progression of motor extremity in ischemic stroke patients. The effectiveness of rtPA therapy was assessed using information in medical records, which showed an increase in the value of limb motor strength in patients evaluated before being given rtPA, 24 and 72 hours after being given rtPA. The patient's extremity motor progress was obtained using the National Institutes of Health Stroke Scale (NIHSS) score. The NIHSS was a systematic research tool for quantitatively measuring acute neurological deficits resulting from stroke. The NIHSS score was checked at patient admission, 24 hours, 72 hours, and when the patient was discharged from the hospital. The NIHSS consisted of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicated normal function in that specific ability, while a higher score indicated some level of impairment.[12] By using this score, the categories were increasing, stable/steady state, and decreasing. Increasing category was decided when there was an improvement in extremity motor skills and muscle strength of the upper and lower extremities (left arm, right arm, left leg, right leg). Stable/steady state if there was no increase or decrease in the degree of motor muscle strength of the extremities. Decrease if there was a reduction in the degree of motor muscle strength of the extremities.

To analyze the effectiveness of rtPA administration with limb motor progress in acute ischemic stroke patients, the marginal homogeneity test was used. The data category was multinominal categorical data of more than 2 x 2. The effect was considered significant if the p-value <0.05. This study used SPSS statistical software to analyze the data.

This research has ethically approved by Health Research Ethics Committee of the Faculty of Medicine, Bandung Islamic University Number 179/KEPK-Unisba/IV/2022 and the Health Research Committee at Al Islam Bandung Hospital Number 018/KEPPIN-RSAI/08/2022.

Results

Of the 42 acute ischemic stroke patients who met the inclusion criteria, most were male (78.6%). The largest age group of patients was the 56–65 years age group (40.5%), followed by the >65 age group at 31%. For history, more patients had hypertension (54.8%), and DM (16.7%), but only 7.1% of patients had a history of heart disease. In addition, more patients had one frequency of stroke (97.6%) (Table 1).

According to the NIHSS Score, before administration of rtPA, all acute ischemic stroke patients experienced muscle weakness.

Table 1 Characteristics of Acute Ischemic Stroke Patients Treated and Given rtPA Therapy at Al-Islam Hospital Bandung, Indonesia in 2019–2021

Variable	n (n=42)	%
Gender		
Male	33	78.6
Female	9	21.4
Age category		
26–35 year	1	2.4
36–45 year	1	2.4
46–55 year	10	23.8
56–65 year	17	40.5
>65 year	13	31.0
History of hypertension		
Yes	23	54.8
No	19	45.2
History of DM		
Yes	7	16.7
No	35	83.3
History of heart disease		
Yes	3	7,1
No	39	92.9
Frequency of stroke		
1x	41	97.6
> 1x	1	2.4
None	0	0

Note: DM= Diabetes Mellitus

After 24 hours of rtPA administration, patients experienced a decrease in muscle strength of 9.5%, a steady state of 28.6%, and an increase in muscle strength of 61.9%. After 72 hours of rtPA, it was found that patients experienced a decrease in muscle strength of 9.5%, a steady state of 16.7%, and an increase in muscle strength of 73.8% (Figure 1).

Patients given rtPA after 24 hours and 72 hours experienced a decrease in muscle strength of 9.5%, a steady state of 28.6% and 16.7%, and an increase in muscle strength of 61.9% and 73.8%. There were no significant different between given rtPA 24 and 72 hours (Figure 1).

Overall, 7.1% of patients after administering rtPA experienced worsening, as many as 16.7% experienced stable conditions and as many as 76.2% experienced improvements. From the results of the Marginal Homogeneity test, it was found that the p-value was 0.000, meaning that there was a significant difference between muscle strength before and after rtPA administration (Figure 1).

Discussion

This study found that most stroke patients were aged 56–65 years. This result is similar to previous study in the UK which stated that the incidence of stroke doubled in the age range above 55 years.[13] Another study has also found that the risk of stroke doubles in every successive decade after the age of 55 years, and 72% of all strokes occur after the age of 65 years.[14]

Based on risk factors, age can increase the incidence of stroke through changes in microcirculation that possibly mediated by endothelial dysfunction, impaired cerebral autoregulation, and neurovascular coupling. Endothelial dysfunction triggers neuroinflammation, impaired cerebral autoregulation can cause microvascular injury, and impaired neurovascular coupling promotes decreased cortical function.[15]

Based on gender, this study showed that the highest incidence of stroke was in the male group. In addition, another study has explored the stroke incidence up to the age of 45 years, men experienced a higher incidence of ischemic stroke and worse functional recovery than women in the same period.[16] However, the risk of ischemic stroke in women begins to rise between the ages of 45 and 54 years, coinciding with the onset of menopause and a decline in circulating steroid hormone levels. This also coincides with the rise in obesity

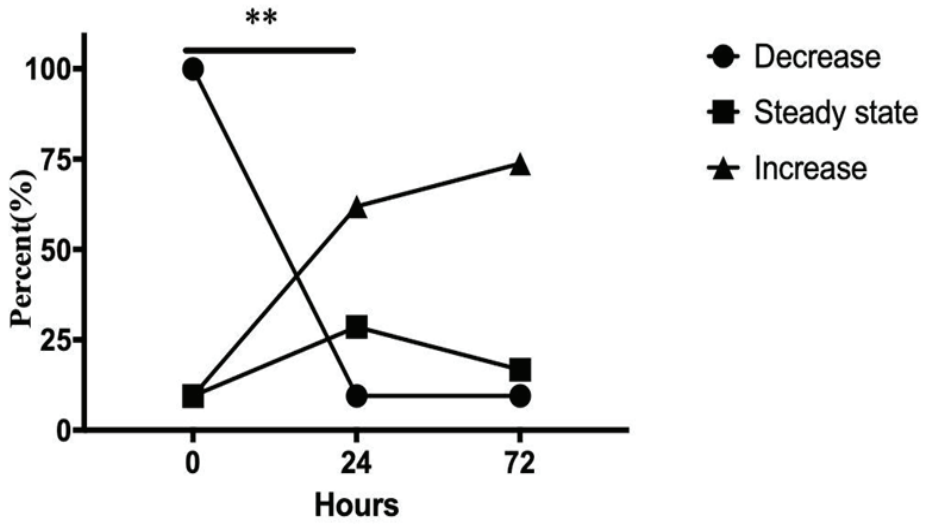

Figure 1 Extremity Motor Strength Before and After Administration of rtPA (24 and 72 hours based on NIHSS Scoring).

Note: n=42 patients, **p value ≤0.01, very significant using marginal Homogeneity tes.

and metabolic syndrome, which contribute to a higher risk of stroke. After age 55 years, the incidence of stroke in men and women is equivalent until age 85 years, when the risk of ischemic stroke is greatest in women.[16]

The results of this study show that most acute ischemic stroke patients have a history of hypertension followed by diabetes mellitus and heart disease. These are the most significant modifiable risk factors for stroke. Approximately, fifty percent of all stroke patients have a history of hypertension. Even in non-hypertensive individuals, the higher the blood pressure, the greater the risk of stroke.[13] Meanwhile, in patients who have a history of diabetes mellitus, people with diabetes have a 1.5–3 times higher the chance of having stroke and a high mortality rate compared to the general population without diabetes. The main reason for metabolic abnormalities is proatherogenic risk factors in the arteries. There are strong indications of large platelet aggregation, hypercoagulability, increased free radical formation, and altered calcium regulation in diabetic patients. As a result, diabetes mellitus can accelerate atherosclerosis.[17] In patients with a history of impaired cardiac function, the incidence of stroke also increases. People with hypertension, coronary heart disease, heart failure, and especially atrial fibrillation are associated with an increased risk of stroke. Atrial fibrillation increases at the age of >70 years.[18]

Based on the results of the study, it was found that 32 patients experienced an increase in the limbs motor strength, seven patients were in steady state, and three patients experienced a decrease after being given rtPA therapy. Also, the data analysis table shows effect of providing rtPA on the motor progress of the patient's limbs in acute ischemic stroke patients. These results are in line with research conducted in Jakarta,[19] and Tadulako,[20] which state that rtPA therapy has been proven to increase the motoric strength of the extremities in patients with acute ischemic stroke, even in patients with acute ischemic stroke with other diseases such as COVID-19.[21]

Globally, the rtPA therapy has been used as a standard treatment for acute ischemic stroke and has been shown to affect outcomes.[22,23] Clinical practice guidelines published by the American Heart Association and American Stroke Association (AHA/ASA) in 2007, and the American College of Chest Physicians in 2008, recommend the use of the rtPA for the treatment of acute ischemic stroke in eligible patients.[24] In another study, it was found that when rtPA was given within the first 3 hours of symptom onset, most of the 100 patients given rtPA experienced minimal or no paralysis after a stroke. This result suggests that rtPA can improve long-term stroke recovery. However, the beneficial impact of rtPA is dependent on time (therapeutic window).[9] This has become a reference in several hospitals to develop a "Code stroke". The code stroke system is a system of quick response efforts and inefficient stroke management in time to facilitate

thrombolysis in the suitable timeframe in cases of acute ischemic stroke to minimize obstacles that cause delays in administering treatment.[25] A study in Canada[26] involving 1,135 (84%) ischemic stroke patients in the country reached the same conclusion. The study showed that in 37% of patients, exceptional clinical outcomes were seen. Only 4.6% of patients experienced symptomatic intracranial hemorrhage, indicating that stroke thrombolysis is a safe and effective therapy for managing stroke.[26]

The increase in limb motor power is due to the thrombolytic effect of rtPA, which will lyse the thrombus. A thrombus consists of fibrin monomers cross-linked via lysine side chains bound by rtPA. The lysine binding site on rtPA is located in the kringle-2 domain, which is why rtPA has a high affinity for binding lysine. Lysine binding to rtPA results in plasminogen activation only near the thrombus, which minimizes activation of circulating plasminogen. The lysine side chain has a high affinity for binding with plasminogen, making the thrombus-rich plasminogen. The rtPA enzyme binds to the fibrin component of the thrombus. It catalyzes the conversion of plasminogen to plasmin through cleavage of the arginine-valine bond at positions 560 and 561 to break up the clot by degrading the thrombus fibrin matrix. Plasmin then breaks down the thrombus into fibrin degradation products due to the action of plasmin proteases in dissolving the thrombus.[27] Therefore, when the blood clot is lysed, it will increase blood flow and improve the function of the brain area that regulates breaking up clots by reducing the thrombus fibrin matrix and the motor function of the extremities.[28]

However, some patients experienced worsening after being given rtPA therapy. This may be caused by risk factors or the patient's medical history. For example, three patients continued to experience decline after being given rtPA. After analysis, it turned out that two patients aged 56 years with a history of hypertension and diabetes mellitus and a patient aged 58 years with laboratory results showing dyslipidemia experienced a decrease in extremity motor strength after being given rtPA. In addition, a 72-year-old patient with a history of hypertension also experienced reduced limb strength after being given rtPA. On average, all three patients had a previous history of stroke. The mechanism of these risk factors can reduce the effectiveness of rtPA therapy is still unclear, but several studies have stated that factors that can exacerbate the outcome of ischemic stroke patients after being given rtPA are diabetes mellitus, hypertension, heart disease such as Atrial Fibrillation, considering these factors can reduce the ability to rtPA for recanalization.[29]

The limitation of this study is that the mechanism of rtpa in stroke has not been explored, so further research is needed to explore the mechanism of this method in vivo or in vitro.

In conclusion, rtPA therapy significantly improves limb motor progression in acute ischemic stroke patients . Currently, there are still very few hospitals in West Java, Indonesia that apply this rtPA therapy. Given the favorable outcomes of rtPA therapy, it is expected that this procedure could be widely implemented in various hospitals in West Java, Indonesia.

The results of this study provide a good contribution to aging-related diseases and cardiovascular conditions, especially stroke, which is one of the critical aging-related diseases and is a prominent problem in the aging population. It is hope that this study can enhance understanding of treatment strategies in management and recovery of stroke, one of which is by carrying out rtPA therapy which has an impact on the recovery of extremity motor function in acute ischemic stroke patients.

References

1. Tu ZY, Ning FH, Yu WJ. Study about recognition of digital meter dial reading based on SVM. Applied Mech Mater. 2014;615:194–7.
2. World Health Organization. The top 10 causes of death [Internet]. 2024. [Cited 2024 December 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
3. Ministry of Health of the Republic of Indonesia. Stroke don't be the one [Internet]. [cited 2023 January 22] Available from: https://www.kemkes.go.id/article/view/20030900004/stroke-don-t-be-the-one.html.
4. United States Centers for Disease Control and Prevention. Stroke facts. [Cited 2023 January 22]. Available from: https://www.cdc.gov/stroke/data-research/facts-stats/index.html.
5. Balasubramanian CK, Clark DJ, Fox EJ. Walking adaptability after a stroke and its assessment in clinical settings. Stroke Res Treat. 2014;2014:591013.
6. Carvalho-Pinto BP, Faria CD. Health,

function, and disability in stroke patients in the community. Braz J Phys Ther. 2016;20(4):355–66.
7. Marquez-Chin C, Popovic MR. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. Biomed Eng Online. 2020;19(1):34.
8. Ramadhoni PD. Trombektomi Mekanik Sebagai Terapi Pilihan Stroke Iskemik Akut Oklusi Pembuluh Darah Besar. Prosiding Ilmiah Dies Natalis Fakultas Kedokteran Universitas Sriwijaya. 2019;1(1):158–62.
9. Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: a systematic review. JAMA. 2015;313(14):1451–62.
10. Stanescu IC, Bulboaca AC, Dogaru GB, Gusetu G, Fodor DM. Predictors for early motor improvement in patients with ischemic stroke. Balneo Res J. 2019;10(3):236–42
11. Yuniadi Y. Intervensi pada stroke non-hemoragik. J Kardiol Indones. 2010;31(3):153–5.
12. National Institute of Neurological Disorders and Stroke. NIH Stroke Scale [Internet]. [Cited 2024 May 26]. Available from: https://www.ninds.nih.gov/health-information/stroke/assess-and-treat/nih-stroke-scale.
13. Murphy SJ, Werring DJ. Stroke: causes and clinical features. Medicine (Abingdon). 2020;48(9):561–6.
14. Kelly-Hayes M, Beiser A, Kase CS, Scaramucci A, D'Agostino RB, Wolf PA. The influence of gender and age on disability following ischemic stroke: the Framingham study. J Stroke Cerebrovasc Dis. 2003;12(3):119–26.
15. Yousufuddin M, Young N. Aging and ischemic stroke. Aging (Albany NY). 2019;11(9):2542–4.
16. Gibson CL, Attwood L. The impact of gender on stroke pathology and treatment. Neurosci Biobehav Rev. 2016;67:119–24.
17. Alloubani A, Saleh A, Abdelhafiz I. Hypertension and diabetes mellitus as a predictive risk factors for stroke. Diabetes Metab Syndr. 2018;12(4):577–84.
18. Rydén L, Sacuiu S, Wetterberg H, Najar J, Guo X, Kern S, et al. Atrial fibrillation, stroke, and silent cerebrovascular disease: a population-based MRI study. Neurology. 2021;97(16):e1608–19.
19. Kurniawan M, Zairinal RA, Mesiano T. Terapi trombolisis intravena pada pasien stroke iskemik dengan awitan kurang dari 6 jam. Neurona. 2014;32(1):1–8.
20. Mutiarasari D. Ischemic stroke: symptoms, risk factors, and prevention. Medika Tandulako. 2019;6(1):60–73
21. Khedr EM, Abdelwarith A, Moussa G, Saber M. Recombinant tissue plasminogen activator (rTPA) management for first onset acute ischemic stroke with Covid-19 and non-Covid-19 patients. J Stroke Cerebrovasc Dis. 2023;32(4):107031.
22. Karaszewski B, Wyszomirski A, Jabłoński B, Werring DJ, Tomaka D. Efficacy and safety of intravenous rtpa in ischemic strokes due to small-vessel occlusion: systematic review and meta-analysis. Transl Stroke Res. 2021;12(3):406–15.
23. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC et al. Scientific rationale for inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. Stroke. 2016;47(2):581–641.
24. Roth JM. Recombinant tissue plasminogen activator for the treatment of acute ischemic stroke. Proc (Bayl Univ Med Cent). 2011;24(3):257–9.
25. Hidayat R, Yasfi HF, Diafri D, Yunus RE, Ramlan AAW, Mesiano T, et al. Membangun sistem code stroke pada dua rumah sakit pendidikan di Indonesia. Neurona. 2020;37(3):194–201.
26. Hill MD, Buchan AM; Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. CMAJ. 2005;172(10):1307–12.
27. Bivard A, Lin L, Parsonsb MW. Review of stroke thrombolytics. J Stroke. 2013;15(2):90.
28. Röttger C, Madlener K, Heil M, et al. Is heparin treatment the optimal management for cerebral venous thrombosis? Effect of abciximab, recombinant tissue plasminogen activator, and enoxaparin in experimentally induced superior sagittal sinus thrombosis. Stroke. 2005;36(4):841–6.
29. Demchuk AM, Tanne D, Hill MD, Kasner SE, Hanson S, Grond M, et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology. 2001;57(3):474–80.