

# Clinical Outcomes of Thrombolytic Therapy in Patients with Mild Stroke: Single-Center Experience in a Tertiary Care Institution

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## Abstract

**Objective:** The term ‘mild stroke’ is used to describe stroke patients with a NIHSS score of 0 to 6. There is still no clear decision regarding the application of iv recombinant tissue plasminogen activator (iv-tPA) to patients who is admitted with an acute ischemic stroke and is in the mild stroke category. In our study, we aimed to analyze the data of patients who applied to our stroke center with an acute mild stroke clinic and received iv-tPA treatment and their three-month follow-up. **Methods:** A total of 47 (age  $69.1 \pm 14.1$ , 28 female) mild stroke patients were included out of 350 patients receiving thrombolytic therapy. Intravenous thrombolysis was initiated with a maximum delay of 4.5 hours in all patients. Patients had a NIHSS score less than 6. NIHSS scores immediately before starting thrombolytic therapy and scores 24 hours after treatment were recorded. Modified Rankin Scale scores (mRS) at admission, 1 and 3 months were recorded. **Results:** NIHSS scores of the patients who received tPA decreased significantly after the treatment ( $p = 0.001$ ). The patients’ 1st and 3rd month mRS scores were statistically significantly decreased according to the mRS scores when they entered the treatment ( $p = 0.001$ ). **Conclusions:** This study highlights the efficacy of iv-tPA in acute ischemic stroke patients with mild symptoms and demonstrates the low risk profile of this therapy.

## Clinical Outcomes of Thrombolytic Therapy in Patients with Mild Stroke: Single-Center Experience in a Tertiary Care Institution

**Keywords:** NIHSS, mild stroke, modified Rankin Scale, thrombolysis, iv-tPA.

**Running title:** Outcomes of Thrombolytic Therapy in Patients with Mild Stroke

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**Informed consent:** Informed consent was obtained from all individual participants included in the study.

**Contribution statement:** All authors contributed the study.

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**Methods:** A total of 47 (age  $69.1 \pm 14.1$ , 28 female) mild stroke patients were included out of 350 patients receiving thrombolytic therapy. Intravenous thrombolysis was initiated with a maximum delay of 4.5 hours in all patients. Patients had a NIHSS score less than 6. NIHSS scores immediately before starting thrombolytic therapy and scores 24 hours after treatment were recorded. Modified Rankin Scale scores (mRS) at admission, 1 and 3 months were recorded.

**Results:** NIHSS scores of the patients who received tPA decreased significantly after the treatment ( $p = 0.001$ ). The patients' 1st and 3rd month mRS scores were statistically significantly decreased according to the mRS scores when they entered the treatment ( $p = 0.001$ ).

**Conclusions:** This study highlights the efficacy of iv-tPA in acute ischemic stroke patients with mild symptoms and demonstrates the low risk profile of this therapy.

**Introduction** National Institute of Health Stroke Scale (NIHSS) is frequently performed for scoring examination data performed before thrombolytic therapy in acute stroke patients. The term 'mild stroke' is used to describe stroke patients with a NIHSS of 0 to 6. There is still no clear decision regarding the application of iv recombinant tissue plasminogen activator (iv-tPA) to patients who is admitted with an acute ischemic stroke and is in the mild stroke category. Today, most of the patients with ischemic stroke do not receive iv-tPA treatment because they do not apply to hospitals within the required time frame (1). In community-based studies, it has been shown that 54.6% of patients who can apply within the first 4,5 hours are in the mild stroke category (2). The recurrent stroke rates of patients in the mild stroke group have been shown to be between 10% and 20% in the first three months, and this recurrence has been noted to be more frequent in a few days after the first stroke (3,4). Thrombolytic therapy (intravenous tissue plasminogen activator, iv-tPA) is one of the most effective treatments in patients with acute ischemic stroke (5,6,7). The iv-tPA treatment can supply clinical improvement in patients by providing reoxygenation in the penumbra tissue with thrombolysis given in the acute phase, as well as protecting the patient from recurrent strokes that can be followed in the first days after stroke (5,6). As the indication of applying iv-tPA to patients in the mild stroke group, the presence of symptoms that often cause disability is mentioned, but this criterion brings about many relative conditions and a large grey zone in the clinic (8). Due to this relative comment, patients who need it or may worsen in the later hours cannot receive thrombolytic therapy. Although the NIHSS is currently used as the most useful patient assessment scale for acute stroke, it may be inadequate, especially in posterior system infarctions, and inadequate in scoring the patient's neurological deterioration (9,10,11). Another criticism to the NIHSS is that the scale may not be sufficient to assess high cortical functions that are impaired or lost in patients with acute stroke (11). Therefore patients who apply to hospitals with acute mild stroke clinic, who cannot receive iv-tPA due to low NIHSS, but worsen the clinic in the following hours or days, constitute an important medical condition. In our study, we aimed to analyze the data of patients who applied to our stroke center with an acute mild stroke clinic and received iv-tPA treatment and their three-month follow-up.

## Material and Methods

The study protocol was approved by the Istanbul Medeniyet University Göztepe Professor Dr. Süleyman Yalçın City Hospital local ethics committee. (2021/0108) Mild stroke patients who were admitted to Istanbul Medeniyet University Neurology Stroke Center between 2018-2020 with an acute ischemic stroke and treated with iv-tPA were retrospectively screened. 350 patients were scanned retrospectively and 50 mild stroke patients receiving thrombolytic therapy were detected. 47 patients were included in the study because they continued their long-term follow-ups in our outpatient clinic. Iv-tPA was initiated with a maximum delay of 4.5 hours in all patients. Patients had a NIHSS less than 6. Patients who underwent mechanical thrombectomy by detecting large vessel occlusion were excluded from the study. Patients who did not continue the follow-up in our hospital and did not come to the outpatient clinic later were not included in the study because their data could not be completed. NIHSS immediately before starting thrombolytic

therapy and scores 24 hours after treatment were recorded. Modified Rankin Scale scores (mRS) at admission, 1 and 3 months were recorded. Age, gender, smoking and alcohol habits, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, coronary artery disease, and previous ischemic stroke histories were taken as risk factors for stroke. Presence of antiaggregant or anticoagulant use during stroke was determined. Strokes were classified as TACI (total anterior circulation infarct), PACI (partial anterior circulation infarct), LACI (lacunar infarct), and POCI (posterior circulation infarct) according to the Oxfordshire Community Stroke Project classification. We classified stroke etiology according to Bamford classification. Patients who had hemorrhagic transformation after thrombolytic therapy were identified.

## Results

Forty-seven mild stroke patients (age  $69.1 \pm 14.1$ , 28 female) from 350 patient who received iv-tPA were included in the study. Characteristics of the patients included in the study are given in Table 1. It was observed that the NIHSS of the patients who received iv-tPA decreased significantly after the treatment ( $p = 0.001$ ). Ischemic stroke risk factors and etiological parameters of the patients are given in table 1. Hemorrhagic transformation was observed in 3 of 47 patients after iv-tPA treatment. Only 1 patient's neurological examination deteriorated after hemorrhagic transformation. 23 (49%) of the patients had partial anterior system infarction, 8 had lacunar syndrome, 16 had posterior system infarction. The patients' NIHSS at admission and 24 hours, mRS scores at admission, 1 month and 3 months are given in Table 2. The patients' 1st and 3rd month mRS scores were statistically significantly decreased according to the mRS scores when they entered the treatment ( $p = 0.001$ ).

## Discussions

In previous study it was demonstrated that iv-tPA treatment is effective on both NIHSS and mRS scores with acute mild stroke patients. This study suggest that mild stroke patients should recieve iv-tPA treatment. Our findings show that patients recieving iv-tPA clinically improve after treatment. First month and third month mRS of patients demonstrated a significant improvement. Acute stroke patients who recieved iv-tPA were mostly recovered completely in the third month.

According to current stroke guidelines, the optimal treatment for acute minor non-disabling stroke patients within the first 4.5 hours is unknown. Prognosis of patients who present with mild symptoms that are considered to be unlikely to cause disability may worsen within days. Therefore stroke patients whose symptoms become apparent in the following hours and patients who experience recurrent strokes in the first days (12). The current guidelines recommend that iv-tPA can be given in patients with low NIHSS and non-disabling deficits. However the strength recommended is weak (class IIb) due to clinical benefit uncertainty (13). Reporting of low therapeutic strength, uncertain benefit and risk of hemorrhage may causes clinicians to avoid administering iv-tPA to this group of patients. Approximately 50 percent of acute stroke patients apply in the mild stroke category; there is uncertainty in the thrombolytic treatment of this large stroke population (2). In the study conducted by Khatri et al., 90-day neurological follow-ups of mild stroke patients who were followed up without thrombolytic therapy were documented. As a result of the study, it was reported that a significant proportion (29%) of disability developed in 90 days in patients with mild ischemic stroke (14).

In Logallo et al.'s study, 1791 patients with acute mild stroke who applied to the stroke center were categorized as patients who received or not recieved iv-tPA and compared each group of patients' risk of intracranial hemorrhage. As a result of the study, it was reported that hemorrhagic transformation developed in 3 patients (1.9%) in the group of receiving iv-tPA and 1 (0.1%) patient in the group of not receiving iv-tPA, and there was no significant risk difference between the two groups (15). In our study, hemorrhagic transformation was observed in 3 of 47 patients and only 1 patient's neurological examination deteriorated after treatment. In the study conducted by Haebarlin et al. in 2019, 3-month functional outcomes of 108 mild stroke patients who received iv-tPA and 262 best medical therapy patients with mild stroke were compared. As a result of the study, it was concluded that patients who received iv-tPA had complete remission more often in their symptoms ( $p < 0.0001$ ) (16).

As a result of the MULTI STAR study conducted for the safety and efficiency of iv-tPA application, it

was stated that mild stroke patients were excluded from thrombolytic therapy due to the risk of cerebral hemorrhage. 25-30% of mild stroke patients suitable for iv-tPA who are not treated due to mild symptoms have poor results in their follow-up. On the other hand mild stroke patients who taken iv-tPA have low hemorrhage risk and favorable outcomes. The results of the study suggest that the treatment of patients with mild stroke is safe and effective (17).

As in similar studies mentioned above, in our study hemorrhagic transformation after thrombolytic therapy was observed in only 3 patients and was found to be very low. Although the NIHSS is used as the most adequate scale in acute stroke, it has limitations (10). There are criticisms that it is inadequate in measuring posterior system infarcts symptoms and high cortical function losses due to cortical infarcts. In our study two patients had internuclear ophthalmoplegia due to posterior system infarct and NIHSS were 0 at admission. In our study, iv-tPA patients with mild stroke significantly improved their functional outcomes according to their 3-month mRS scores. Likewise, it was observed that NIHSS calculated with acute stroke symptoms significantly decreased after iv-tPA treatment.

## Conclusion

In conclusion, this study highlights the efficacy of iv-tPA in acute ischemic stroke patients with mild symptoms and demonstrates the low risk profile of this therapy.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## References

1. Del Zoppo GJ, Saver JL, Jauch EC, et al. Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator. A Science Advisory From the American Heart Association/American Stroke Association. *Stroke*. 2009;40(8):2945-8.
2. Dhamoon MS, Moon YP, Paik MC, et al. Long-term functional recovery after first ischemic stroke: The Northern Manhattan Study. *Stroke* 2009; 40: 2805–2811.
3. Chandratheva A, Geraghty OC, Rothwell PM, Poor performance of current prognostic scores for early risk of recurrence after minor stroke. *Stroke* 2011;42, 632–637.
4. Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis a er emergency department diagnosis of TIA. *JAMA*. 2000;284, 2901–2906.
5. Tissue plasminogen activator for acute ischemic stroke. e National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995; 333, 1581–1587.
6. Cocho D, Belvís R, Martí-Fàbregas J, et al. Reasons for exclusion from thrombolytic therapy following acute ischemic stroke. *Neurology* . 2005;64, 719–720.
7. Khatri P, Kleindorfer DO, Devlin T, et al. Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial. *JAMA*. 2018;10;320(2):156-66.
8. Powers WJ, Rubinstein AA, Ackerson T et al. 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*. 2019;50:344–418

9. Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864–870.
10. Muir KW, Weir CJ, Murray GD, et al. Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke*. 1996;27:1817–1820.
11. Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the NIH Stroke Scale. *Stroke*. 2000;31: 858 – 862
12. Barber PA, Zhang J, Demchuk AM, et al. Why are stroke patients excluded from tPA therapy? An analysis of patient eligibility. *Neurology* 2001; 56: 1015–1020
13. William J. Powers, Alejandro A. Rabinstein et al, 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, 30 Oct 2019, *Stroke*. 2019;50:344–418
14. Khatri P, Conaway MR, Johnston KC; Acute Stroke Accurate Prediction Study (ASAP) Investigators. Ninety-day outcome rates of a prospective cohort of consecutive patients with mild ischemic stroke. *Stroke*. 2012 Feb;43(2):560-2. doi: 10.1161/STROKEAHA.110.593897. Epub 2011 Nov 3. PMID: 22052513; PMCID: PMC3426999.
15. Logallo N, Kvistad CE, Naess H, et al. Mild stroke: safety and outcome in patients receiving thrombolysis. *Acta Neurol Scand Suppl*. 2014;(198):37-40. doi: 10.1111/ane.12235. PMID: 24588505.
16. Haerberlin MI, Held U, Baumgartner RW, et al. Impact of intravenous thrombolysis on functional outcome in patients with mild ischemic stroke without large vessel occlusion or rapidly improving symptoms. *Int J Stroke*. 2020;15(4):429-437.
17. Sørensen SB, Barazangi N, Chen C, et al. Generalized Safety and Efficacy of Simplified Intravenous Thrombolysis Treatment (SMART) Criteria in Acute Ischemic Stroke: The MULTI SMART Study. *J Stroke Cerebrovasc Dis*. 2016 May;25(5):1110-1118. doi: 10.1016/j.jstrokecerebrovasdis.2016.01.016. Epub 2016 Feb 18. PMID: 26897101.

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