

## Case Report

# Low Dose Thrombolytic Therapy in the Eldest Filipino at 96 years-old

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**ABSTRACT:** Thrombolytic therapy using intravenous tPA (Tissue Plasminogen Activator) or alteplase is the standard treatment in patients presenting within 4.5 hours of ischemic stroke, but elderly patients have mostly been excluded from acute revascularization studies due to hemorrhagic complications. The concern for the hemorrhagic transformation in Asian populations has led to the use of low-dose alteplase (0.6mg/kg) instead of the standard dose at 0.9mg/kg. Shunsaku et al. in 2014 showed feasibility and efficacy of low dose thrombolysis. Stroke risk increases exponentially with increasing age, and there is a low rate of thrombolysis among the extremely old patients (>85 years old) with ischemic stroke. We report a 96 year old Filipino female, with multiple co-morbidities, who had an acute right middle cerebral territory ischemic stroke, with a total National Institutes of Health Stroke Scale (NIHSS) of 19, who received low dose thrombolytic therapy with significant improvement of neurologic status without adverse outcomes. Low-dose alteplase can be a safe and effective thrombolytic strategy in the extreme elderly population.

**Keywords:** Stroke, Thrombolysis, Elderly Acute Ischemic Stroke, Low-Dose Recombinant Tissue Plasminogen Activator, rTPA

## INTRODUCTION

Human nervous tissue is rapidly and irretrievably lost as stroke progresses and therapeutic interventions should be emergently pursued. The typical patient loses 1.9 million neurons each minute in which stroke is untreated.<sup>1</sup> Stroke is one of the leading causes of death and is the leading cause of permanent disability and disability-adjusted loss of independent-life years. Thrombolytics increase the chance of a good outcome by 30%.<sup>2</sup> This treatment can be administered up to 4.5 hours of symptom onset in many patients with ischemic stroke. The Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) concluded that patients < 80 years old are appropriate candidates for thrombolysis.<sup>3</sup>

It is favored to use low-dose alteplase when patients are thought to be at high risk of bleeding such as in older patients, those with decreased renal function, or when endovascular treatment is anticipated.<sup>4</sup> To our knowledge, there are no local published studies of low-dose recombinant tissue plasminogen activator (rt-PA) therapy for patients, ≥ 80 years old with acute ischemic stroke (AIS).

## CASE REPORT

This is a case of a 96 year old female, Filipino, right handed, known hypertensive, with permanent atrial fibrillation (CHADSVASC 6 HASBLED 2), functionally dependent on most activities of daily living, and needing assistance with ambulation. Patient had a chief complaint of sudden onset left sided weakness. Patient was last seen well and asymptomatic at 2 hours 30 minutes prior to consult, when patient was still eating dinner and conversant. Few minutes later, she had sudden onset of slurring of speech, preferential movement of her right extremities, then had decreased sensorium. She was then immediately brought to the tertiary hospital ER at around 2 hours and 45 minutes post

ictus, where the rapid response team called the Brain Attack Team was activated. Neurologic exam revealed the patient was drowsy, severely dysarthric, with left homonymous hemianopsia by visual threat, pupils 3mm equally brisk and reactive to light, preferential gaze to the right, left central facial palsy, hemiplegic on left upper and lower extremities, and with Babinski on the left. The total National Institutes of Health Stroke Scale (NIHSS) was 19. An emergency cranial CT scan done at around 3 hours and 30 minutes post ictus showed acute infarct on the right middle cerebral territory. Thrombolysis was then initiated after consent was given, at a low dose of 0.6mg/kg dose, compared to the standard 0.9mg/kg, to reduce possible hemorrhagic complications in this age group. During the hospital course, patient showed improvement of neurologic status. Her sensorium improved. She still had mild dysarthria with a midline gaze. Motor examination showed improved strength of the left upper and lower extremities as patient was able to raise extremities against gravity. Three months post thrombolysis, and with adequate neurorehabilitation, patient had minimal residual on her left side and her motor strength was back to baseline.

## DISCUSSION

In the extreme elderly population, thrombolysis is considered an option but poses several risks as they are thought to have higher propensity to have hemorrhagic complications.<sup>5</sup> In one study in Italy done by Toni, D et al., the efficacy and safety of the use of intravenous thrombolysis using the standard dose 0.9mg/kg in patients aged >80 years was evaluated and compared with that in younger individuals to determine the incidence of good functional outcomes three months after the stroke.<sup>6</sup> Good outcomes were defined as those with modified Rankin Scale (mRS) scores of 0–2, and poor outcomes included death or dependency (mRS scores of 3–5). According to the study, no

difference in the incidence of intracerebral hemorrhage was observed between the groups. Additionally, the positive and negative outcomes of the thrombolytic treatment were not statistically different between the two cohorts after three months. Those aged >80 years had a statistically higher mortality rate than the younger group. The NIHSS score predicted mortality and poor outcomes in the older group. However, the final outcome of this study suggested that thrombolytic therapy should also be available to elderly patients, i.e. those aged >80 years.

Although the risk of stroke increases with age, some physicians remain cautious about administering thrombolytic therapy to very elderly patients who experience an acute ischemic stroke. Mateen et al. were the first to examine alteplase treatment in patients aged >90 years, using retrospective data from four medical centers between 1999 and 2008.<sup>7</sup> The authors examined clinical neurological symptoms, complications, and outcomes of patients with acute ischemic stroke after alteplase treatment. The study included eleven women, with ages ranging from 90–101 years. The range of time to alteplase treatment was 90–180 minutes. The patients had a range of NIHSS scores of 5–28. Nearly all patients were mobile before the stroke (median mRS score, 1; median Barthel Index score, 95); only one patient had minimal movement restrictions. After 30 days of observation, two patients had a positive outcome, and two others had slight disabilities. The majority of patients died or had severe mobility problems, and three had asymptomatic cerebral hemorrhages. Thus, alteplase treatment did not appear to improve outcomes. However, better results were obtained with alteplase treatment in patients with acute ischemic stroke aged >90 years in another recently published study by Sandercock et al.<sup>8</sup> In this study, 111 patients with acute ischemic stroke aged >90 years were treated with rt-PA. The majority of patients aged >90 years benefited from treatment with rt-PA within the 3-hour treatment time frame in this study.

A meta-analysis done by van Asch CJ et al. showed that the East Asian population have had higher prevalence of hemorrhage compared to Western population.<sup>9</sup> The concern for the hemorrhagic transformation in Asian populations has led to use of low-dose alteplase (0.6mg/kg) instead of the standard dose of thrombolysis at 0.9mg/kg alteplase.<sup>4</sup> A study done by Takanayagi et al, in Japan evaluated the safety and effectiveness of low-dose recombinant tissue plasminogen activator (0.6 mg/kg) therapy for elderly acute ischemic stroke patients ( $\geq 80$  years old) in the pre-endothelial era.<sup>10</sup> This study showed that the incidence of symptomatic intracerebral hemorrhage was not significantly different between the younger (4.3%) and older (0%) groups ( $p = 0.61$ ). The recanalization rate of the occluded artery was also similar between the younger (54%) and older (50%) groups ( $p = 0.78$ ). The rate of a low mRS score (e.g. 0–2) three months after stroke was significantly higher in the younger (44.3%) than in the older group (11.8%) ( $p = 0.013$ ). Low-dose rtPA therapy appears

to be as safe and feasible for adult  $\geq 80$  years old as it is for younger people. Three months following tPA therapy, approximately 30% of patients were neurologically normal or near normal; 30% had mild to moderate neurological deficits; 20% had moderate to severe neurological deficits; and 20% died.<sup>2</sup>

This case of a 96-year-old female Filipino given thrombolysis for acute ischemic stroke shows that the alternative low-dose alteplase strategy has comparable effectiveness and safety to the standard. There was no further deterioration of functional status. There was no significant adverse effect like bleeding during infusion. It could be a practical option at least for ischemic stroke patients of East Asian ancestry who are expected to have a higher risk of cerebral hemorrhages. Despite the anticipated worse outcomes among the older patients compared to the younger patients, an association between thrombolysis and improved outcomes can be observed in the very elderly. This case suggests that age should not be an exclusion criterion for alteplase treatment for acute ischemic stroke.

### Conclusion

Elderly patients have mostly been excluded from acute revascularization studies due to higher hemorrhagic complications.<sup>5</sup> In general, older patients with stroke have worse outcomes compared to the younger population.<sup>11</sup> While thrombolysis clearly shows a benefit in fit and independent older patients who meet the criteria to participate in clinical trials, many elderly patients have significant physical and cognitive co-morbidities, and the risk/benefit ratio for thrombolysis is less well defined. In our opinion, however, even small benefits, i.e. regaining the ability to speak or swallow, improving mobility, can make a big difference in quality of life in this age group.

This 96-year-old Filipino female who was successfully treated with a low dose thrombolytic for ischemic stroke is the first reported case in the Philippines in this age group. Alteplase therapy should not be categorically denied to elderly patients with acute ischemic stroke, based solely on patient age. Because the threshold of 80 years is arbitrary for thrombolysis, physicians should weigh the risks and benefits of intravenous alteplase to treat acute ischemic stroke in elderly patients on an individual basis.

This case report is limited only to the patient's hospitalization. The functional status within six months post thrombolysis could give a more sufficient assessment of the patient's clinical recovery after stroke.

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