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Intravenous Thrombolysis in Patients 90 Years or Older with Moderate to Severe Acute Ischemic Stroke Increases Ambulation at Discharge and Is Safe: A Prospective Cohort Study from a Single Center in Santiago, Chile

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Keywords
Acute stroke · Nonagenarians · Thrombolytic therapy · Mortality · Elderly

Abstract

Introduction: The World Health Organization predicts that the global population aged 60 years and older will double by 2050, leading to a significant rise in the public health impact of acute ischemic stroke (AIS). Existing stroke guidelines do not specify an upper age limit for the administration of intravenous thrombolysis (IVT), although some suggest a relative exclusion criterion in patients aged ≥80 in the 3–4.5-h window. Many physicians avoid treating these patients with IVT, argumenting high risk and little benefit. Our aim was to investigate the efficacy and safety of IVT treatment in patients with non-minor AIS aged ≥90, admitted to our institution. The primary efficacy endpoint was the ability to walk at discharge (mRS 0–3), and the primary safety endpoints were death and symptomatic intracranial hemorrhagic transformation (sIHT) at discharge. ***Methods:*** Patients with AIS aged ≥90 admitted to our center from January 2003 to December 2022 were included. They were selected if had an NIHSS ≥5, were previously ambulatory (prestroke mRS score 3 or less), and arrived within 6 h from symptom onset. Those treated or not with IVT were compared with univariate analysis. ***Results:*** The mean age was 93.2 (2.4) years, and 51 (73.9%) were female. The admission mRS and NIHSS were 1 (IQR 0–2) and 14 (IQR 7–22), respectively. Thrombolyzed patients had a shorter time from symptom onset to door and lower glycemia on admission. IVT was associated with a higher proportion of patients achieving mRS 0–3 at discharge ($p = 0.03$) and at 90 days ($p = 0.04$). There were no differences between groups in the risk of death ($p = 0.55$) or sIHT ($p = 0.38$). ***Conclusion:*** In this small sample, ambulatory patients aged ≥90 with moderate or severe AIS treated with IVT had increased odds of being able to walk independently at discharge than those not treated, without safety concerns.

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Plain Language Summary

Elderly population is expected to continue to increase, with the accordingly growth in ischemic stroke burden, and the reperfusion therapies can still be debated in relation to its efficacy and safety, particularly in nonagenarian patients. This manuscript summarizes our experience in patients 90 years or more with moderate to severe AIS. We retrospectively reviewed in our prospective registry 69 nonagenarian patients with ischemic stroke recruited from January 2003 to December 2022, previously ambulatory, and admitted within a 6-h time window. The mean age of the total group was 92.3 (SD 2.4%), and 73.9% were women. Patients that received lytic drugs had lower glycemia at admission and had shorter time from symptom onset to door. We found that IVT was associated with higher probability of being able to walk in nonagenarian patients at discharge ($p = 0.035$) and at 3 months ($p = 0.048$) after ischemic stroke, without differences in hemorrhagic transformation or death, compared to patients without thrombolysis. Therefore, age in previously ambulatory patients should not be an argument to exclude them from thrombolysis.

Introduction

In 2020, the number of people aged 60 years and older outnumbered children younger than 5 years old [1]. This significant elderly population growth is expected to increase the public health burden in acute ischemic stroke (AIS). Pooled analyses have demonstrated a clear benefit of intravenous recombinant tissue-type plasminogen activator (rtPA) in patients aged 80 years or older, achieving excellent functional outcomes and similar mortality, compared to placebo [2].

Existing international stroke treatment guidelines do not specify an upper age limit for intravenous thrombolysis (IVT). However, in numerous countries, guidelines tend to view age as a relative exclusion criterion for patients aged 80 and above within the 3–4.5-h treatment window [3–5]. Despite comparable bleeding risk to younger groups and observed higher probabilities of improved functional outcomes compared to non-thrombolyzed patients of the same age, some guidelines continue to emphasize age-related considerations [6–8]. The aim of this study was to investigate the safety and efficacy of rtPA treatment in previously ambulatory patients aged 90 years or older with moderate or severe AIS admitted to our institution.

Materials and Methods

Study Design and Participants

In this retrospective review of a clinical cohort, we included all consecutive patients with an AIS within 6 h from symptom onset (ensuring the inclusion of those who underwent subsequent thrombectomy), admitted to Clínica Alemana de Santiago from January 01, 2003, to December 31, 2022, who were 90 years or older, with a National Institutes of Health Stroke Scale (NIHSS) score of 5 or more, were able to walk independently (prestroke modified Rankin scale [mRS] score 3 or less), and consented to participate in our prospective Stroke registry (Registro de Enfermedades Cerebrovasculares Clínica Alemana [RECCA]). We compared thrombolyzed to non-thrombolyzed patients.

Variables were prospectively collected. AIS was defined according to current national and international definitions, confirmed by non-contrast brain computed tomography (CT) scan and/or diffusion-weighted magnetic resonance imaging [3, 9]. Occluded vessels were confirmed with CT or MRI angiography. The Alberta Scale Programme Early CT Score (ASPECTS) was reviewed by the on-call neurologist, stroke neurologist, and/or the stroke fellow. Risk factors had to be present before stroke symptoms. Functional status was defined according to the mRS, where scores 0–2 indicate independence (from no symptoms to slight disability), scores 3–5 indicate moderate-severe disability (from being able to walk with help, needing assistance in bodily needs, or being bedridden), and score 6 indicates death. Sedentary lifestyle was defined as less of 3 h of exercise per week and alcohol consumption as intake of more than 30 g per week.

Symptomatic intracranial hemorrhagic transformation (sIHT) was defined according to ECAS III classification: clinical deterioration defined as an increase of ≥4 points on NIHSS or that led to death, with any hemorrhage in CT/MRI, being the predominant cause of the neurological deterioration. Patients were thrombolyzed according to the institutional protocol, based on national and international guidelines [3, 9]. Patients are thrombolyzed in an early window if they meet the inclusion criteria of any focal neurological deficit measurable by NIHSS within 5 h of symptoms onset or last time seen well and without any of the exclusion criteria. In an extended window, the EXTEND trial criteria are used if presenting until 9 h of last time seen well or wake-up strokes, selecting patients with RAPID AI® (iSchemiaView) software for perfusion-CT analysis. There is no specific restriction or any modification to our protocol based on age alone. The use of alteplase or tenecteplase depends on center availability at the time of patient admission.

Outcomes

The primary efficacy outcome was defined as mRS of 0–3 at discharge. Safety outcomes were death and sIHT also at discharge.

Statistical Analyses

Sociodemographic characteristics, cardiovascular risk factors, primary efficacy, and safety endpoints were compared by thrombolytic therapy, using χ^2 or Fisher's test for frequencies. Normality in variables was assessed with the Shapiro-Wilk test. *t* test was used for normally distributed continuous variables and Mann-Whitney U test for non-normally distributed continuous variables in the univariate analyses. A sensitivity analysis was performed using predicted mRS at 3 months based on a regression model derived from other populations

Table 1. Baseline characteristics

Variable	Thrombolyzed (*N* = 37)	Non-thrombolyzed (*N* = 32)	*p* value
Age (SD), years	93.5 (2.6)	92.9 (2.2)	0.38
Female, *n* (%)	28 (75.7)	23 (71.9)	0.47
mRS upon admission, median [IQR]	1 [0–1]	2 [0–3]	0.08
Vascular risk factors			
Hypertension, *n* (%)	26 (70.3)	25 (78.1)	0.32
Hypercholesterolemia, *n* (%)	10 (27.0)	9 (28.1)	0.56
Diabetes mellitus, *n* (%)	3 (8.1)	5 (15.6)	0.27
Current smoking, *n* (%)	1 (2.7)	3 (9.4)	0.25
Atrial fibrillation, *n* (%)	13 (35.1)	16 (50.0)	0.15
Heart failure, *n* (%)	5 (13.5)	2 (6.3)	0.28
History of any cardiopathy, *n* (%)	22 (59.5)	22 (68.8)	0.29
Use of anticoagulants in the last month, *n* (%)	5 (13.5)	10 (31.3)	0.06
Sedentary lifestyle, *n* (%)	28 (84.8)	25 (86.2)	0.59
History of alcohol use, *n* (%)	3 (8.1)	4 (12.5)	0.42
Clinical characteristics at admission			
Mean systolic blood pressure (SD), mm Hg	162 (26.9)	162 (29.6)	0.97
Mean time from symptom onset to door (SD), min	102.7 (55.4)	163.7 (96.7)	0.002
NIHSS score upon admission, median [IQR]	14 [7–21]	20 [7–22]	0.88
Door to needle time (SD), min	52.5 (23.0)	(–)	(–)
ASPECTS, median [IQR]	9 [8–10]	8 [7–10]	0.07
Arterial occlusion at CT angiography, *n* (%)	18 (58.1)	14 (70.0)	0.29
Laboratory findings at admission			
Mean glycemia (SD), mg/dL	112 (19)	122 (42.9)	0.009
Thrombolytic used			
Alteplase, *n* (%)	29 (78.4)	(–)	(–)
Tenecteplase, *n* (%)	8 (21.6)	(–)	(–)

SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Programme Early CT Score; mRS, modified Rankin scale.

Table 2. Primary efficacy and safety outcomes, unadjusted

	Thrombolysis (*N* = 37)	Non-thrombolysis (*N* = 32)	*p* value
mRS score 0–3 at discharge, *n* (%)	23 (62.2)	12 (37.5)	0.035
mRS score 0–3 within 90 days, *n* (%)	20 (54.1)	10 (31.3)	0.048
Symptomatic intracranial hemorrhage, *n* (%)	3 (6.8)	1 (2.3)	0.38
Death, *n* (%)	5 (11.3)	5 (11.6)	0.55

mRS, modified Rankin scale.

developed by our stroke research group (unpublished), because the RECCA registry did not follow patients at 90 days before February 2017. This model was based on univariate analysis and other prediction tools published previously [10, 11] and included the following variables: age, sex, current smoking; mRS and NIHSS upon admission; and mRS at discharge. Missing values were treated by the listwise deletion approach.

All statistical analyses were performed with Stata 18.0. An alpha error <0.05 was considered significant. The paper is reported according to the STROBE guidelines.

Results

Of 3,500 patients screened in our registry between 2003 and 2022, a total of 69 (2.0%) met the inclusion criteria. Mean age was 93.2 (2.4) years, and 51 (73.9%) were female. Median admission NIHSS was 14 (IQR 7–22), and median previous mRS was 1 (IQR 0–2). Baseline demographic, vascular risk factors, clinical and laboratory characteristics on

Table 3. Observational trials of IVT in patients 90 years or older with AIS

Reference	Study type	*N*	Intervention	Control	Outcome	Functional outcome	sIHT	Mortality
Kauffman et al. [6]	Retrospective cohort	211	Thrombolysis and/or thrombectomy (64)	No therapeutic intervention (147)	mRS ≤2 sIHT mortality (at discharge)	Significant improvement (not described) (p = 0.001)	5.3% vs. 1.4% (NS)	12.5% vs. 10.9% (NS)
Balestrino et al. [7]	Retrospective cohort	52	Thrombolysis (11)	No therapeutic intervention (41)	mRS (ordinal) sIHT mortality (at 90 days)	2.3±2.7 vs. 4.7±1.8 (p = 0.014)	0% in both groups (NS)	36.4% vs. 57.9% (NS)
Behrouz et al. [8]	Prospective cohort	227	Thrombolysis (122)	No therapeutic intervention (105)	mRS 0–3 sIHT mortality (at 90 days)	OR 0.61 (95% CI; 0.39–0.96)	4.9% vs. 3.8% (NS)	43% vs. 33% (NS)
Gomes et al. [12]	Retrospective cohort	167	Thrombolysis and/or thrombectomy (77)	No therapeutic intervention (90)	mRS 0–2 sIHT mortality (at 90 days)	17.1% vs. 26.1% (NS)	14.3% vs. 3.3% (p = 0.011)	39.5% vs. 25.3% (NS)
Sagnier et al. [13]	Retrospective cohort	78	Thrombolysis (37)	No therapeutic intervention (41)	mRS 0–2 (at 90 days) sIHT mortality (at 7 days)	5% vs. 7% (NS)	22% vs. 0% (NS)	22% vs. 10% (NS)

mRS, modified Rankin scale; sIHT, symptomatic intracranial hemorrhagic transformation.

admission, and clinical features during hospitalization and discharge of both groups are shown in Table 1.

In univariate analysis, IVT was associated with significantly less mean time from symptom onset to door, lower glycemia upon admission, and higher proportion of patients achieving mRS 0–3 at discharge (p = 0.035) and at 90 days (p = 0.048). There were no differences between groups in the risk of death (p = 0.55) or sIHT (p = 0.38) (Table 2).

Discussion

We report that in patients 90 years or older who were previously ambulatory with moderate or severe AIS treated with IVT there was an increased probability of being able to walk independently at discharge, compared to those not thrombolyzed. Similar results have been reported previously. Behrouz et al. [8] demonstrated an OR 0.61 (95% CI: 0.39–0.96) in favor of rtPA treatment and Balestrino et al. [7], a better probability of mRS 0–2 at 90 days (54.5 vs. 18.4%, p = 0.047) (Table 3).

Contrarily, other studies have shown no outcome differences with rtPA administration [12, 13]. Possible causes for discrepant results include small numbers of patients and defining primary outcomes as being independent (mRS 0–2) at 90 days, which is difficult to achieve in this population.

Death rates have been demonstrated to be similar between groups in other studies [6–8, 12, 13], according to randomized evidence [2]. Our study has several limitations and possible biases. The observational cohort design based on usual clinical practice in a single center is subject to selection bias in the choice of treatment. As such, these results are only associations and hypothesis generating and do not imply causality. The sample size is small and so has low power to detect weak associations. We used mRS at discharge as primary endpoint and predicted mRS at 90 days. The general efficacy of thrombolysis has been shown in RCT at 90 days, and even though sensitivity analysis confirmed our results, they were based on a non-published prediction model that includes discharge mRS.

Conclusion

Thrombolyzing previously ambulatory patients of 90 years or older with moderate or severe AIS was associated with an increase in probability of being able to

walk dependently at discharge compared to no IVT, without safety concerns. Age alone should not be an exclusion criterion in this population.

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by Comité Ético Científico de la Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, approval number 2010-11, and written informed consent was obtained in every patient as per local regulatory law request.

Conflict of Interest Statement

Pablo E. González and André I. Aguirre have no conflicts of interest to declare. Alejandro M. Brunser reports lectures supported by Boehringer Ingelheim. Verónica V. Olavarría reports receiving research grant from Boehringer Ingelheim and Clínica Alemana de Santiago during the conduct of the study. Pablo M. Lavados reports research support from Clínica Alemana and Boehringer Ingelheim; research grants from The George Institute and Clínica Alemana de Santiago during the conduct of the study; unrestricted research grants from Lundbeck and Boehringer Ingelheim; personal fees from AstraZeneca and Bayer as SOCRATES and ESUS NAVIGATE trials national leader; and a Chilean Government research grant for the ÑANDU project outside the submitted work.

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Author Contributions

P.E.G., P.M.L., A.I.A., A.M.B., and V.V.O. contributed to the design and interpretation of the data and drafted the manuscript; P.E.G. contributed to the data collection of the study; P.E.G. and P.M.L performed the statistical analysis; P.M.L., A.M.B., P.E.G., and V.V.O. contributed to interpreting results and reviewing the manuscript and approved the final version of the manuscript. V.V.O. has primary responsibility for final content.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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