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Original Article

Observational study of thrombolytic treatment for acute stroke in patients older and younger than 80 years: experience from one hospital in Bogotá, Colombia, 2007-2014

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ABSTRACT

Background: we depict the experience with the use of thrombolysis for acute ischemic stroke in a tertiary center in South America. **Objective:** to describe the main outcomes in our population of patients aged less and older than 80 years treated with recombinant tissue plasminogen activator. **Materials and Methods:** retrospective observational study. We described the main variables and the difference in outcome accounting for age. **Results:** 70 patients were included. 51.4% of the patients were women, 22.8% were older than 80 years. The average window time was 70 minutes and the average door-to-needle time was 90 minutes. Hypertension, dyslipidemia and previous stroke were the most common risk factors. Favorable outcome Modified Rankin Scale ≤2 was present in 25% of the patients older than 80 years and 53.7% in the population younger than 80 years (p=0.009). Mortality was present in 31.2% of the patients older than 80 years and in 5.5% of the patients younger than 80 years (p=0.005). Symptomatic intra-cerebral hemorrhage was found in 6.25% of the patients older than 80 years (p=0.65), compared to 3.7% in the younger than 80 years. **Conclusions:** we found that intravenous thrombolysis still had benefit in people older than 80 years. Significant differences in symptomatic intra-cerebral hemorrhage were not found, however, a greater mortality in patients older than 80 years was. These findings of our experience of recombinant tissue plasminogen activator use in real life are consistent with other latinamerican publications. **MÉD.UIS. 2017;30(3):21-30.**

Keywords: Stroke. Thrombolytic Therapy. Aged, 80 and over. Risk Factors. Prognosis.

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Estudio observacional sobre tratamiento trombolítico del infarto cerebral agudo en pacientes mayores y menores de 80 años: experiencia de un hospital en Bogotá, Colombia, 2007-2014

RESUMEN

Introducción: describimos la experiencia con el uso de trombólisis para el infarto cerebral isquémico agudo en un centro terciario en América del Sur. **Objetivos:** describir los principales resultados en nuestra población de pacientes menores y mayores de 80 años tratados con activador recombinante de plasminógeno tisular. **Materiales y Métodos:** estudio observacional retrospectivo. Se describieron las principales variables y se determinaron los resultados según la edad. **Resultados:** se incluyeron 70 pacientes. Se encontró que 51,4% eran mujeres y 22,8% eran mayores de 80 años. El tiempo de ventana promedio estuvo en 70 minutos, así como el de puerta-aguja de 90 minutos. La hipertensión, dislipidemia y accidente cerebrovascular previo fueron los factores de riesgo más comunes. En el 25% de los pacientes mayores de 80 años y el 53,7% de los menores de 80 años, tuvieron un resultado favorable en la Escala Modificada de Rankin ≤ 2 (p = 0,009). La mortalidad estuvo presente en el 31,2% de los pacientes mayores de 80 años y en el 5,5% de los pacientes menores de 80 años (p = 0,005). La hemorragia intracerebral sintomática fue de 6,25% en los pacientes mayores de 80 años, frente a los menores de 80 años 3,7% (p = 0,65). **Conclusiones:** se encontró que la trombólisis todavía presenta beneficio en personas mayores de 80 años. No se encontraron diferencias en cuanto a la hemorragia intra-cerebral sintomática, pero se presentó una mayor mortalidad en los mayores de 80 años. En esta experiencia el uso de rt-PA en la vida real es consistente con otras publicaciones latinoamericanas. **MÉD.UIS. 2017;30(3):21-30.**

Palabras clave: Accidente Cerebrovascular. Terapia Trombolítica. Anciano de 80 o más Años. Factores de Riesgo. Pronóstico.

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Introduction

Every year, 15 million people worldwide have a stroke. Of those, one-third dies, and one third is left with a long-term disability[1-3]. World mapping has shown an increase in the absolute number of people having a stroke, demonstrating that the global burden of cerebrovascular disease is continually increasing with more than 100% increment in stroke incidence in developing countries[4]. 85% of the stroken burden worldwide comes from low and middle income countries, like Colombia and most of the South American Countries[5,6]. Some investigators have predicted an emerging pandemic of non-communicable chronic conditions like cardiovascular disease, including stroke[7], mainly due to an ageing population.

In Colombia, South America, life expectancy has been growing since 2004. The last data from 2015 showed that men have a life expectancy of 70.5 years and 77.6 years for women with an average of 73.9 years for the whole country. The projected number of people ≥ 80 years of age in 2020 will be 800 885 compared with 501 077 in 2005[8]. Although there is no data available about the incidence of stroke in Colombia, it is expected to increase due to the ageing population, a phenomenon that has started to hit developing countries as well.

87% of strokes are the result of a vascular occlusion[9], either because of thrombotic or embolic events that lead to vascular blocking and compromised cerebral flow. The ischemic event leads to adenosine triphosphate (ATP) deficiency in brain tissue, resulting in release of excitatory neurotransmitters and a rise of calcium influx, which in turn induce free radicals production, ultimately leading to neurotoxicity and loss of cell viability[10].

According to the Framingham Heart Study, among patients older than 65 years who survived an acute stroke and were evaluated six months after the event, 50% of them had hemiparesis, 30% needed assistance to walk, 19% had aphasia, 35% had depressive symptoms and 26% were institutionalized in a nursing home. Stroke is the second or third cause of death in developing countries, but the first cause of disability[11]. It causes between 0 to 358 disability adjusted life years lost calculated for our country[5]. The estimated direct and indirect costs in the United States for stroke in 2008 were almost $298 million of dollars[1]. Those results elucidate the diversity of disability and dependence[1] seen in stroke survivors.

Thrombolysis improves several outcomes in patients with Acute Ischemic Stroke (AIS). Tissue Plasminogen Activator (t-PA) acts by enhancing the conversion of inactive plasminogen to active plasmin, which

in turn causes dissolution and lysis of fibrin clots. Recombinant Tissue Plasminogen Activator (rt-PA) was designed as a molecule that selectively activates fibrin-bound plasminogen[12]. In 1996, a landmark clinical trial demonstrated that intravenous (IV) rt-PA administered within three hours of the ischemic stroke onset improved clinical outcomes at three months. Based on the results of this phase III trial, the Food and Drug Administration (FDA) approved rt-PA for the treatment of AIS[13]. Furthermore, in 2008 the European Cooperative Acute Stroke Study III (ECASS III) showed that IV rt-PA given between 3 to 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with AIS[14]. The results of ECASS III led to the extension of the thrombolytic window, but patients older than 80 years were excluded from participating in the extended window time[14]. Currently, IV thrombolytic therapy is widely recommended as the standard of care for AIS in most practice guidelines[15,16]. For every patient admitted in the first 3 hours of symptoms onset there is no age limit for rt-PA administration (Level of Evidence A, Class I)[15].

Safety and efficacy data of rt-PA in the patients older than 80 years of age is limited, since they are poorly represented in clinical trials due to stringent exclusion criteria[7]. Evidence regarding the benefits of rt-PA administration in people < 18 years is scarce; moreover, the benefit in people older than 80 years of age remains controversial, mainly due to limitations in the designs of the studies performed in this population and the increased risk of intracranial bleeding[17].

The European Stroke Organisation (ESO) guidelines recommend administering rt-PA to patients over 80 years of age in selected cases[18]. The Canadian Stroke Best Practice Recommendations guideline advises that the decision to treat rests on clinical judgments and patient/family wishes[19]. The Colombian guideline encourages the use of rt-PA in patients over 80 years old in the extended period (3 hours to 4.5 hours) to achieve better outcomes[20].

Our aim is to describe the common practice with thrombolytic treatment for AIS in the treated observed population stratified by age, considering younger and older than 80 years in terms of risk factors, attention times, complications, disability and mortality in the first seven days. Our hypothesis is that the patients ≥ 80 years have a worse outcome compared with younger counterpart in terms of morbidity and mortality in the first week after stroke, and obtain less benefit from using rt-PA. We would like to show the experience of rt-PA use in Colombia because there is a scant amount of publications about this important and divisive topic coming from our country.

Materials and methods

This is a retrospective observational study developed at University Hospital Fundación Santa Fe (UHFS), which is a tertiary care center, located in the northeast area of Bogotá. The UHFS has a two hundred and five beds capacity, and a low rate of stroke admissions of approximately 50 to 80 patients a year. The stroke center at our Neurology Department implemented the main inclusion/exclusion criteria for thrombolysis from the National Institutes of Neurological Disorders Stroke (NINDS) trial criteria[13] and adopted the American Heart Association/American Stroke Association (AHA/ASA) Guidelines for indications for IV rt-PA[15]. The protocol was submitted and approved by the local Institutional Review Board (IRB)/ Corporative in Ethics and Research Committee. The hospital protocol for thrombolysis takes place in the emergency and radiology department during the acute phase. We check the inclusion – exclusion criteria for thrombolysis and a decision is made whether or not to administer the medication or intervention (See Figure 1). The stroke code was introduced in 2008 as an alert system of the stroke team.

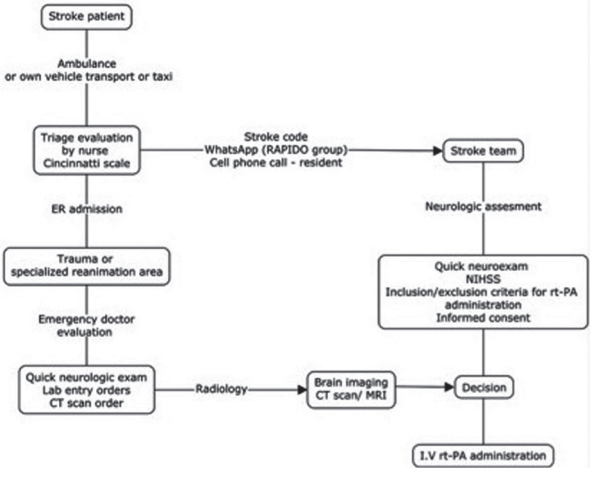


Figure 1. Acute Stroke Hospital Protocol
ER: Emergency, NIHSS: National Institute of Health Stroke Scale, rt-PA: Recombinant Tissue Plasminogen Activator, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, I.V: Intravenous
Source: Authors.

All patients admitted to the Neurology Department of UHFS between january 2007 and july 2014 were identified and included in the study if they met the

following inclusion criteria: patients older than 18 years of age, diagnosed with AIS confirmed by neuroimaging, an important measurable neurological deficit present, symptom onset in the previous 4.5 hours and treated with rt-PA, intravenously or endovascularly (pharmacological or mechanical), if IV rt-PA was contraindicated or considered too dangerous. Exclusion criteria were patients who had been less than 48 hours in the emergency room and subjects with intracranial hemorrhage. No informed consent was necessary in this study due to the less than minimum risk for subjects and retrospective data review, but removal of patient identifiers was performed. We used a standard data collection form to retrieve data from the electronic chart of each subject. Data collection was performed by the investigators in a predefined excel spreadsheet. We performed data validation in three different opportunities.

We present baseline characteristics and important time periods such as time from onset of symptoms to arrival to the emergency room (Window Time), time to first neurology encounter, time since admission to rt-PA administration (Door-to-Needle Time), time from admission to neuroimaging studies (Door-to-Image), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI); the time delay from imaging to image interpretation (Door-to-Interpretation), stroke severity by National Institute of Health Stroke Scale (NIHSS) at admission; complications, mortality, length of stay and early outcomes such as the NIHSS at discharge and the Modified Rankin Scale (mRS).

Regarding the NIHSS, the neurology resident or senior neurologist in charge of the patient determined the score on admission, 24 h after rt-PA therapy and at discharge or at day seven, whichever happened first. A decrease of four or more points in the NIHSS was considered clinical improvement; an increase of four or more points was considered clinical deterioration.

Using the clinical findings and diagnostic imaging (CT or MRI) obtained on admission and 24 hours after symptoms onset (or earlier if clinical deterioration), we determined the affected vascular territory and the etiology according to the Trial of Org 10 172 in Acute Stroke Treatment (TOAST)[21] scale, after completing test evaluation and at discharge. We used the definition of Safe Implementation of Thrombolysis in Stroke - Monitoring Study (SITS-MOST) for symptomatic intracerebral hemorrhage based on the clinical deterioration of more than four NIHSS points from admission or from the lowest NIHSS obtained between admission and 24 hours and a local or remote parenchymal hematoma type 2 in the control brain CT at 24 hours[22].

Statistical analysis

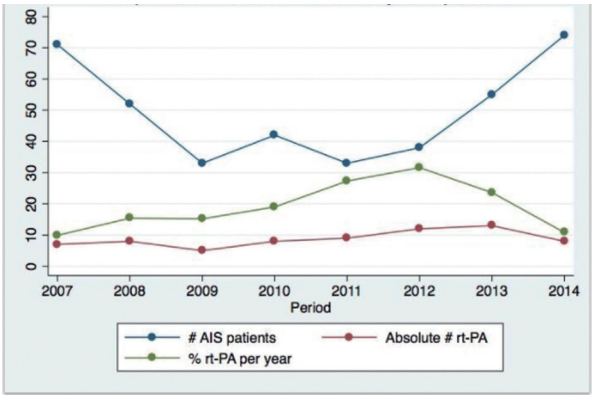
Data was collected on an electronic spreadsheet (Microsoft ® Excel ®, Mac Version 14.4.3 -140616-, 2011), and then exported to STATA 11.2 (StataCorp ®, 2009). The baseline characteristics of our population were presented using frequencies and proportions for categorical variables and central tendency measures for continuous variables. Distribution of continuous variables was assessed by Shapiro-Wilk test of normality. We performed the frequency (percentage) of rt-PA use for every one-year period. No sample size was calculated due to the descriptive nature of the study that analyzed the whole population that received rt-PA during the eight-year period in UHFS.

The cohort was divided in two groups: < 80 years and ≥ 80 years. We evaluated the most important prognostic factors as well as clinical and outcome variables. We performed Chi-Square or Fischer Test for categorical outcomes, Mann and Whitney U test for nonparametric analysis of continuous variables and the student t-test for variables displaying a normal distribution. mRS was dichotimized as 0-2 and ≥3 and we compared this categorical outcome between the two predefined age groups. A statistical significance was established with an alpha level of <0.05.

Results

A total of 398 subjects had a stroke and attended the hospital between 2007 and 2014, of those patients 17.8% (n=70) received IV rt-PA or endovascular intervention. In both 2009 and 2011 we had the lowest number of patients, 33, of which 5 patients (15.2%) and 9 patients (27.3%), respectively, received intervention. The highest number of patients was 74 in 2014 but only 7 subjects were treated (9,5%) (See Graph 1).

In the selected cohort of 70 patients we found the mean age of 69 years with a range of 35 to 97, with 36 women (51%). The main risk factors were hypertension in 75.6% followed by dyslipidemia in 40% and in third place previous stroke (38.5%). The stroke code was activated in 17% of cases (See Table 1).



Graph 1. Stroke center thrombolytic experience
AIS: Acute Ischemic Stroke, rt-PA: Recombinant Tissue Plasminogen Activator
Source: Authors.

Table 1. Demographic Characteristics

Variable	N	Mean	Range
Risk Factors			
Age	70	68.9	35-97
Gender-Female	36	51.4	
Hypertension	53	75.7	
Coronary artery disease	16	22.8	
Diabetes mellitus	10	14.2	
Dislypidemia	28	40	
Atrial Fibrillation	14	20	
Previous stroke	28	38.5	
Stroke Code activation	12	17.1	
Admission Systolic Blood Pressure (mmHg)	70	150.5	89-220
Admission Diastolic Blood Pressure	70	83	34-120
Vascular Territory			
Left-Middle Cerebral Artery	20	45.5	
Right-Middle Cerebral Artery	16	36.3	
Posterior Circulation	6	13.6	
Multiple Territories	1	2.2	
Anterior Cerebral Artery	1	2.2	

Source: Authors.

The most frequent arterial territory affected was the left middle cerebral artery in 20 patients (45.5%). Timing calculation for the whole cohort showed that the patients arrived to the hospital after 78.2 minutes with a range of 0 to 257 minutes. The first contact with the emergency physician was within 10 minutes and with the stroke team in 39 minutes. The lecture of the imaging was done in 87.6 minutes and the door to needle time was 90 minutes and the onset to treatment time was 168 minutes. The NIHSS value at admission was 11.7 and at discharge of 7. The mean mRS at discharge was 2.2. The mortality was 8.5% (n=6) and the length of stay was 10.4 days (See Table 2).

Table 2. General Times and Scales

Variable	N	Mean	SD	Median	Range
Window Time (min)	70	78.2	59.7	70	0-257
Time to first doctor (min)	70	10	18.3	15.4	0-107
Time to stroke team (min)	67	39.1	31.2	33	0-132
Time to imaging (min)	63	37.3	30.1	32	1-164
Time to imaging lecture (min)	65	87.6	91.9	56	2-479
Door to needle time (min)	64	98	44.2	90	22-291
Onset to treatment time (min)	67	168	66.7	166	58-390
rt-PA dose (mg)	59	55.6	27.7	63	0-90
NIHSS admission	69	11.7	5.5	11	1-25
NIHSS 24 hours	63	7.9	7.9	5	0-42
NIHSS discharge	59	7	8	4	0-42
Discharge mRS (7th day)	59	2.2	2	1	0-6
Inhospital mortality (7th day)	6	8.5			
Length of stay (days)	70	10.4	7.4	8	1-36

rt-PA: recombinant tissue Plasminogen Activator. NIHSS: National Institute of Health Stroke Scale. mRS: modified Rankin Scale
Source: Authors.

In our sample we observed 77.2% of the patients < 80 years old (n=54) and 22.8% patients ≥ 80 years (n=16). We found some differences in risk factors between both age groups like gender and atrial fibrillation. In the older population 75% were females and in the younger population 44.4%. Furthermore, in the groups of <80 years of age eight patients had atrial fibrillation (14.8%), while only six patients (37.5%) had it in the >80 years old group (p=0.03) (See Table 3).

Table 3. Distributions of risk factors between the observed subjects

	Distribution by age		p value
	< 80 y	≥ 80 y	
% (n)	77.2 (54)	22.8 (16)	<0.001
Age range. years old	35-80	81-97	<0.001
Gender %. female (n)	44.4 (24)	75 (12) C7	0.03
Hypertension % (n)	72.2 (39)	87.5 (14)	0.21
CAD % (n)	18.5 (10)	37.5 (6)	0.11
Diabetes % (n)	12.9 (7)	18.7 (3)	0.56
Dyslipidemia % (n)	42.5 (23)	31.2 (5)	0.41
AF % (n)	14.8 (8)	37.5 (6)	0.04
Prior stroke % (n)	40.7 (22)	31.2 (5)	0.49
Weight-Kg	74.2	66.3	0.17

CAD: coronary artery disease AF: Atrial Fibrillation
Source: Authors.

The most common etiology was large vessel disease in both groups, 46.3% (n=25) in patients <80 years and 56.2% (n=9) in those ≥ 80 years, followed by cardioembolic source in 38.9% (n=21) in the younger population compared with 37.5% (n=5) in the older population (p=0.76). Middle cerebral artery vascular territory was the most commonly involved in both groups, the left artery within the age <80 years 46.3% (n=25), and the right for those patients ≥80 years 43.7% (n=7), followed by the posterior circulation with 12.5% (n=2) in those patients aged ≥ 80 years and 12.9% (n=7) in the patients <80 years (*p*=0.35).

The time from onset to treatment was less than 180 minutes in 62% for the patients < 80 years and for 57.1% in patients ≥ 80 years (*p*=0.94). The stroke code was activated in the 31.2% of patients ≥80 years and 12.9% in the <80 years (*p*=0.08). A longer stay was observed with a trend between the older population with a mean of 13.5 days and 9.5 days for the younger population (*p*=0.07). An improvement of more than four points in NIHSS was found in 74% of the patients <80 years of age similar to the 75% in the patients ≥80 years (*p*=0.94) (See Table 4).

The administration of rt-PA was exclusively IV in 88% of the cases (n=62), with two patients that started treatment with IV rt-PA followed by endovascular treatment (2.86%) and two patients treated with rt-PA intraarterially plus IV rt-PA (2.86%). Just four subjects had contraindication for IV rt-PA and were treated with endovascular devices only (5.71%) (*p*=0.37).

Table 4. Time intervals of attention to thrombolyzed stroke patients and outcomes

Time period - minutes	Distribution by age		
Mean values	< 80 y	≥ 80 y	p value
Window Time	76.9	78.6	0.93
Door-to-First doctor	14.2	19.5	0.73
Door-to-Stroke Team	38	43	0.8
Door-to-CT scan	38.1	34.5	0.54
Door-to-Interpretation	88.8	83.5	0.96
Door-to-Needle Time	98.2	97.5	0.64
Stroke Code Activation -n(%)	7(31.2)	5(12.9)	0.08
Main Outcome Stroke Scales			
NIHSS admission	10.9	14.1	0.03
NIHSS 24 hours	7.4	9.7	0.34
NIHSS improvement -n(%)	40(74)	12 (75)	0.94
NIHSS 7th day	6.5	8.5	0.39
mRS 7th day	1.97	3.1	0.01
Lenght of Stay -days-	9.5	13.5	0.07

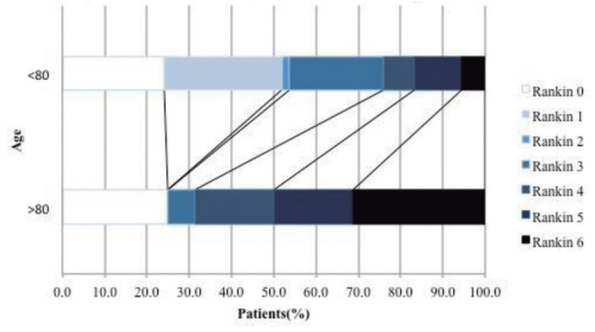
CT: Computarized Tomography. NIHSS: National Institute of Health Stroke Scale. mRS: modified Rankin Score.
Source: Authors.

In patients ≥ 80 years, we found that 25% of the patients had a favorable outcome, with a mRS ≤ 2, and 53.7% for those <80 years (*p*=0.009) (See Graph 2). 43.7% (n=7) had a mRS between 3 to 5 in the older population and 40.7% (n=22) in the younger population (*p*=0.06), with a mortality of 31.2% in patients ≥ 80 years compared with 5.5% in patients <80 years (*p*=0.005). We found two symptomatic brain hemorrhages, one in the <80-year-old group (3.7%) and one in the patients ≥ 80 years (6.25%) (*p*=0.65).

Discussion

In this observational study, we found that in the older population patients were more commonly women, and atrial fibrillation was more frequent as a risk factor. Higher NIHSS at admission and higher mortality compared with the younger population was also determined. Stroke frequency increases every

decade starting at 45 years until 84 years, being more frequent in men and after 85 years of age becoming more frequent in women[23]. Atrial fibrillation is an important risk factor in the older population, more so in women ≥ 80 years. This explains more severe and disabling strokes at this age with higher mortality and stroke recurrence rates[24,25], which correlates with our results.



Graph 2. Modified Rankin Scale-Day 7
Source: Authors.

A good functional prognosis, defined as a mRS between zero and two, among subjects ≥ 80 years who were treated with rt-PA in the first six hours was also found in 27.2% of the treatment group and in 23.4% of the allocated placebo group (p=0.07)[26] in the meta - analysis that included the Third International Stroke Trial (IST-3) results. Our results showed that 25% of the older group treated with rt-PA had an good functional prognosis at day seven, compared with 53.7% in the younger population indicating a benefit in both age groups however, clearly larger in the patients <80 years[27-38].

Previous reports of other papers have also shown that mortality in stroke is related to the annual volume of patients. In institutions with medium volume as ours[39], a similar mortality has been reported ranging between 2.4 to 34.8% in a Canadian study. Our study shows a mortality range between 5.5% and 31.2%. This is consistent with the expected mortality for our annual volume of patients and for the mortality reported in prior trials.

We compared our results with other hospitals in Latin America like University Hospital of San Ignacio[40] in Bogotá and the Hospital de Base do Distrito Federal[41] in Brasilia and the Joinville cohort study in Brazil[42], however the main information was taken from the Hospital de Base do Distrito Federal table paper (See Table 5). Our study period was the longest among the other published papers; with a larger proportion of women and a similar range of NIHSS with the hospital last mentioned. The Joinville study included patients with NIHSS > ten points due to the design of the study, indicating more severe strokes. We reported increased improvements of NIHSS > four points but with similar disability, measured by mRS ≤ two, comparable to the study in University Hospital of San Ignacio, but improved compared to the Brazilian studies. We believe that gathering this data is an important step towards describing the effectiveness of rt-PA in this population for South America, which includes mainly developing countries.

Table 5: Comparisons between Hospitals In South America regarding rt-PA administration

Characteristics	Study (Hospital/Institution/Region)			
	UHFS	UHSI	HBDF	Joinville
Number of subjects	70	24	32	82
Study period (years)	8	2	1	2
Mean age (years)	69	NR	59	71.1
Variation	(35-97)	NR	(31-86)	NR
Gender (% male)	48	20	59	53.7
NIHSS variation	(4-25)	(8-20)	(3-24)	(13.5-21)
Window Time (min)	70 (0-257)	NR	118 (11-228)	77
Door to needle time (min)	90 (22-291)	NR	89 (32-244)	NR
Onset to treatment (min)	166 (58-390)	NR	195 (60-270)	170
Significant improvement in NIHSS (%)	50	NR	50	NR
Favourable result at discharge (mRS 0-2) (%)	55	50	44	37
Hemorrhagic transformation (%)	4	NR	6	12
Mortality (%)	9	12	13	39

UHFS:University Hospital Fundacion Santa Fe, UHSI: University hospital of San Ignacio
HBDF:Hospital de Base do Distrito Federal
rt-PA:recombinant tissue Plasminogen Activator. NIHSS: National Institute of Health Stroke Scale. mRS: modified Rankin Score. NR: non-reported
Source: Authors.

Thereby we decided to compare our results with similar non-randomized controlled studies as shown[27-37]. They compared treated patients older and younger than 80 years, with better disability outcomes measured by mRS in the youngest population, with no striking difference in symptomatic intracerebral hemorrhage, but with a remarkable intra-hospital mortality and at three months (See Table 6). These results were also corroborated by a meta-analysis that showed a combined OR for symptomatic intracerebral hemorrhage of 1.27 [CI 95%, 0.85 to 1.91] (ns), mortality at three months OR=3.18 [CI 95%, 2.48 to 4.09] and mRS OR=0.52 [CI 95% 0.42 to 0.64] for better outcome for the youngest[35]. They presented as a possible explanation for increasing mortality in the older population more severe deficits at presentation[7], as in our cohort of ≥ 80 years with an average of admission NIHSS of 14 points compared with 11 points in the < 80 years. Severity could also be explained by the number of associated comorbidities in the octogenarian population as described previously[43].

Table 6: Data extraction of observational studies of thrombolysis in older and younger than 80 years

Study (year)	n	Age		mRS ≤ 1		OR	mRS ≤ 2		OR	SICH		Mortality	
		<80	>80	<80	>80		<80	>80		<80	>80	<80	>80
Van Oostenbrugge (2006)[27]	184	139(76)	45(24)	45%	27%	2.2 [1.0-4.0]	63%	36%	3.13[1.5-6.3]	2.9%	11.1%	16.0%	40.0%
Tanne (2000)*[28]	189	159(84)	30(16)	30%	37%	1.3[0.5-3.6]	62%	54%	ns	6.0%	3.0%	8.0%	20.0%
Uyttenboogaart (2007)[29]	142	111(78)	31(22)	36.1%	16.1%	ns	ns	ns	2.6[0.8-8.7]	3.6%	9.7%	10.8%	12.9%
Boulouis (2012)[30]	400	302(75)	98(25)	ns	ns	ns	70%	52%	0.5[0.3-0.8]	10.0%	12.0%	6.0%	10.0%
Gómez - Chocó (2008)[31]	157	108(68)	49(32)	37%†	25%†	ns	ns	ns	ns	6.0%	6.0%	10.0%	6.0%
Toni (2008)[32]	248	207(83)	41(17)	ns	ns	ns	58.5%	44.0%	ns	2.4%	2.4%	10.6%	34.1%
Berrouschot (2005)[33]	228	190(84)	38(16)	46.8%	26.3%	ns	61.6%	31.6%	ns	2.6%	2.6%	5.3%	21.1%
Chen (2005)[34]	183	127(69)	56(31)	ns	ns	ns	ns	ns	ns	6.3%	7.1%	11.0%	20.0%
Ringleb (2005)¥[35]	478	378(79)	90(21)	44.8%ᵗ	20.3%ᵗ	ns	ns	ns	ns	5.3%	6.9%	14%ᵗ	29.7%ᵗ
Sylaja (2006)[36]	1135	865(76)	270(24)	40%	26%	ns	66.6%	44.7%	ns	4.6%	4.4%	18.2%	35.3%
Meseguer (2008)[37]	129	107(83)	22(17)	37%	27%	ns	ns	ns	ns	7.5%	13.6%	11.2%	27.3%
Mouradian (2005)[38]	96	65(67)	31(23)	ns	ns	ns	58.5%	16.1%	0.14[.05-0.4]	6.2%	9.7%	9.2%	32.3%
Bayona (2017)	70	54(77)	16(13)	ns	ns	ns	53.7%	25.0%	2.8[.75-10.4]¶	3.7%	6.2%	5.5%	31.2%

ns:not specified. mRS:modified Rankin Scale. OR: Odds Ratio SICH:Symptomatic Intracerebral Hemorrhage
***Multicenter study**
† mRS<1 if basal mRS≤2
ᵗPatients selected by CT
¥ Data from study and also meta-analysis from previous studies
¶Post-hoc analysis
Source: Authors.

To the best of our knowledge this is probably the first English report of thrombolytic therapy in our country and also is the largest series of rt-PA use published in Colombia. Data showed a low annual volume of patients between 2007 and 2014, with an average number of nine patients every year that were treated with rt-PA, meaning that 17.6% of the patients benefited from rt-PA treatment. Our study showed

almost triple the average use of thrombolysis in AIS patients than in the United States, 3.4% to 5.2%, reflecting the characteristics of our center[44]. UHFS is a tertiary center with a Stroke Unit and stroke code. It has been described that having an alert system, significantly reduces the time to neurology staff assessment, time to CT scan, time to laboratory testing and door to needle time, and that increases the rate of rt-PA administration[45].

Limitations

Due to the study design and sample size, we expect this study could be basal data generated in the stroke field that is limited in our country and in South America. Although our study involves a small cohort it shows data for a longer time period (eight years) as compared to other previous published data in South America. Unfortunately, we did not include a crucial outcome variable such as the place of discharge of the subjects because this varies consistently in different age strata as shown in previous studies[43]. We also missed in the study design the combination and severity of different conditions that worsen the prognosis in this advanced age population.

We are also aware that our center's characteristics are not generalizable of the vast majority of the hospitals in our country. We expect that a high population of patients live in areas with low access to health care and few hospitals have the training and resources to administer rt-PA. Therefore, we presume that other hospitals in our country might have lower rt-PA utilization rates and perhaps worst functional outcomes and higher mortality rates.

Conclusions and recommendations

Despite the lack of a randomized controlled trial in this age range population, our study suggests that thrombolysis still has a beneficial effect in patients older than 80 years, when they are compared with patients younger than 80 years in terms of disability at discharge. We found that mortality is higher at seven days in the older population, probably due to factors related to stroke, patient fragility and comorbidities. Although a small sample size this study serves as a stepping-stone in understanding and better characterizing our population in regards to rt-PA use and benefits especially that is poorly studied in population older than 80 years. Given the scarcity of evidence in our country we strongly believe that patients and families should be advised and informed about the goals of therapy, potential complications and realistic outcomes.

Ethic considerations

The study was approved by the Institutional Review Board (IRB)/ Corporative in Ethics and Research Committee of the University Hospital Fundación Santa Fe de Bogotá.

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Conflict of interest

The authors declare that there is no conflict of interest.

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