Chapter 4

Intravenous Thrombolysis for Acute Ischemic Stroke in a High Complex Regional Hospital

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Additional information is available at the end of the chapter

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Abstract

Background: Intravenous thrombolysis (IVT) with alteplase (tissue plasminogen activator) is the standard pharmacological treatment in acute ischemic stroke (AIS), reducing disability in patients.

Aim: To report the results of a thrombolysis protocol taken during 6 years in a regional public hospital at Temuco, Chile.

Material and methods: Data from 231 consecutive patients aged 67.1 ± 13.1 years (58.9% men) who were treated with IVT, from May 2012 until April 2018, were analyzed.

Results: The median door-to-needle time was 71 min (interquartile range = 53–102). The median National Institute of Health Stroke Scale (NIHSS) scores on admission and at discharge were 13 and 4 points, respectively. At discharge, 27% of hospitalized patients had a favorable outcome, defined as having 0 to 1 points in the modified Rankin scale. Symptomatic intracerebral hemorrhage and mortality rates were 5.7 and 13.1%, respectively. The thrombolysis rate rose from 0.7% in 2012 to 5.5% in 2018.

Conclusions: The implementation of 24/7 neurology shifts in the Emergency Department allowed us to increase the amount and quality of IVT in our hospital, as measured by the rate of thrombolysis and by process indicators such as door-to-needle time.

Keywords: fibrinolytic therapy, stroke, time-to-treatment, thrombolytic therapy, tissue plasminogen activator, alteplase

1. Introduction

Stroke is the leading cause of disability and the second cause of death worldwide [1]. More than two-thirds of the global burden of stroke occurs in developing countries, where

the average age of patients is 15 years younger than in developed countries [2]. In the period 2000–2008, the total incidence rates in low- and middle-income countries exceeded the level of stroke incidence in high-income countries by 20% for the first time [3]. Stroke has become one of the main health problems in many countries of Latin America and the Caribbean [4].

In Chile, cerebrovascular diseases (CBVD) are the leading cause of death, with a rate of 50.6 deaths per 100,000 inhabitants in 2011. In addition, they are the first specific cause of disability-adjusted life years (DALY) in older than 74 years and the fifth between 60 and 74 years [5]. Acute ischemic stroke (AIS) is the most frequent cause of CBVD in Chile and represents approximately 65% of all cerebrovascular events [6]. CBVD is the leading cause of death in Chile and accounted for 9% of all deaths in 2010 [6]. About 8888 people died in Chile in 2010 due to CBVD, and 26,072 were hospitalized with the diagnosis of CBVD in Chile in 2009.

The PISCIS population study conducted in Iquique during 2000–2002 gave the following information: the total incidence adjusted for age for a first stroke was 140.1 per 100,000 inhabitants. The incidence rates per 100,000 inhabitants according to the type of stroke were: 87.3 for cerebral infarction, 27.6 for intracerebral hemorrhage, and 6.2 for subarachnoid hemorrhage. About 93% of the new brain strokes occur in people older than 45 years: the average age was 66.5 years and 56% of them were men. Mortality at 1 month after a first cerebral infarction was 19% and mortality at 6 months was 28%. About 18% of people are left with a moderate or severe dependence at 6 months after a cerebral infarction [7]. The prevalence of CBVD, according to the National Health Survey (NHS) in 2016–2017 is 2.6% in the general population, and rises to 8.2% in ≥65 years [8]. A slight increase was observed when comparing the prevalence estimated in the 2009–2010 NHS, with 2.2 and 8.1%, respectively [9].

2. Stroke in the Araucanía region

The incidence rate of CBVD, calculated as a diagnosis of hospital discharge, in the period 2001–2010, in the Araucanía Sur Health Service, was 961.3 per 100,000 inhabitants/year [10].

According to the data from the 2017 census, the largest number of indigenous people in Chile is concentrated in the Araucanía Region. About 34.0% of respondents mentioned belong to an indigenous or native people, which is significantly higher than 12.8% at national level [11]. Furthermore, according to the 2009–2010 ENS, the Araucanía region has the highest prevalence of high systolic blood pressure compared to the other regions. On the other hand, the Ninth region (Araucanía), along with the Fifth, Seventh, and Eighth, presents double the mortality by stroke compared with the rest of the regions of Chile. Most of the increased risk would be given by the prevalence of poverty, diabetes, sedentary lifestyle, and overweight [12].

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AIS is the most frequent reason for neurological consultation in the adult emergency service (AES) of the Dr. Hernán Henríquez Aravena Hospital (HHHA) in Temuco-Chile, accounting for 30.7% of the attentions performed by the neurologist [13]. The HHHA is located in the heart of the city of Temuco (310,020 inhabitants), capital of the Ninth region of Araucanía, about 670 km south of Santiago de Chile, has 730 beds, and is the only hospital of high complexity of the Araucanía region, and serves a beneficiary population of approximately 800,000 inhabitants. The HHHA neurology unit does not have its own service and depends on the internal medicine service. Our hospital lacks a stroke unit [14].

3. Intravenous thrombolysis in acute ischemic stroke

Intravenous thrombolysis (IVT) with alteplase (tissue plasminogen activator), administered up to 4.5 h from the onset of symptoms, is the reference pharmacological treatment in AIS, reducing the likelihood of dependence patients [15, 16]. The effectiveness of IVT is highly time dependent. Around one in three patients treated with alteplase within 3 h of symptom onset, and one in six treated within 4.5 h, achieves significant benefit [17, 18]. Since 1996, IVT has been the standard management for acute AIS in developed countries. However, IVT has been used in the treatment of AIS on small scale in Latin America and the Caribbean but not on a national basis. The time from stroke onset to hospital arrival is crucial for thrombolysis to be effective, and studies in Lima-Peru, Montevideo-Uruguay, and Joinville-Brazil reported delays in hospital admission. Cost is also an issue, especially for public-health systems, which hampers planning of thrombolysis for a subgroup of patients with ischemic stroke in Latin America [4]. Although the implementation of IVT was rapid in the Chilean private health system [19] since 1997, it was not until 2011 that the first experience of an IVT protocol was reported in a public hospital in the country [20]. Currently, the rate of thrombolysis in large private clinics in Santiago-Chile is 12%, but in public hospitals, it is 6% [5]. This gap seems significant because 80% of the population in Chile is served in the public health system.

4. Intravenous thrombolysis in the HHHA

Since May 2012, IVT has been performed in the HHHA, which has face-to-face neurologists 24/7 in the emergency department since July 2013 [14]. The following is a series of consecutive patients who received IVT, between May 2012 and April 2018. The IVT protocol was based on the NINDS (1995) and ECASS III (2008) studies, that is, thrombolysis within 3 h, and between 3 and 4.5 h, respectively [15, 16]. In addition, modifications were made considering the most recent medical literature [21] and local experience, particularly in relation to age (over 80 years) and the relevance of some relative contraindications [22, 23]. **Table 1** shows the inclusion, exclusion, and precaution criteria of the IVT protocol.

Inclusion criteria
• Neurological symptoms for a period less than 4.5 h, with defined start time
• Neurological deficit measurable by the NIHSS scale[a]
• Computed tomography of the brain without signs of intracranial hemorrhage
• Signed informed consent
Exclusion criteria
• Ischemic stroke within the last 3 months
• Traumatic brain injury or central nervous system surgery in the last 3 months
• Acute myocardial infarction within the last 21 days
• Major surgery in the last 14 days or organ biopsy
• History of intracranial hemorrhage
• History of coagulopathy (hemophilia, von Willebrand)
• Gastrointestinal or urinary tract bleeding in the last 21 days
• Use of oral anticoagulants with INR[b] > 1.7 or new anticoagulants in the last 48 h
• Seizure at the onset of symptoms (except diffusion confirms infarction)
• Noncompressible arterial puncture in the last 7 days
• Lumbar puncture in the last 7 days
• Pregnancy or delivery during the last month
• Known antecedents of neoplasia with risk of bleeding
• Systolic BP[c]> 185 mmHg and/or diastolic BP > 110 mmHg refractory to intravenous medication
• Evidence of systemic bleeding
• Suspicion of septic embolism or infectious endocarditis
• Rapidly improving symptoms
• NIHSS score < 4
• Glucose concentration < 50 or > 400 mg/dl
• Prolongation of partial-thromboplastin time > 40%
• Platelet count < 100,000/mm^3
• Hematocrit < 25%
• Prothrombin time > 15 s
• Hemorrhage or early hemorrhagic transformation
• Extensive constituted infarction
Caution criteria
• Age over 80 years
• Severe neurological deficit (NIHSS score > 22)
• Early signs of extensive infarction (ASPECTS[d] score < 7)
[a]National Institute of Health Stroke scale
[b]International Normalized Ratio
[c]Blood pressure
[d]Alberta Stroke Program Early CT Scan score.

Table 1. Criteria for inclusion, exclusion, and precaution for intravenous thrombolysis [14].

5. Results

In total, 231 patients were treated in the period May 2012–April 2018. The average age of the patients was 67.7 years (SD = 12.6), with a median of 69 years and about 56.6% of the patients were male (N = 136). The clinical characteristics of the thrombolysed patients are shown in **Table 2**.

Regarding the time parameters, the median of the start-to-door time was 105 min interquartile range (IQR): 70.5–156.5. The median door-to-needle time (DNT) was 71 min (IQR: 53–102). The median onset-to-needle time was 185 min (IQR: 136–235). The median of the NIHSS scale at admission was 13 points (IQR: 8–18). In 79 patients (34.2%), the DNT was ≤60 min. Likewise, there was a constant decrease in DNT and a progressive increase in the percentage of patients treated in less than 60 min from their admission to emergency (**Table 3**). In 110 patients (47.6%), thrombolysis was started within 3 h of evolution of the AIS.

For the first 106 patients treated until April 2016, the clinical classification of the AIS, according to the Oxfordshire criteria, was: 44.3% of TACI (total anterior) infarcts stand out, 35.9% of PACI (partial anterior) infarcts, 15.1% of POCI (posterior) infarcts, and 4.7% of LACI (lacunar) infarcts. The etiologies of the AIS, according to the TOAST classification, are the following: 23.4% of atherothrombotic cause, 35.9% of cardioembolic cause, 5.7% by arterial dissection, 5.7% of lacunar infarctions, and 29.3% of indeterminate cause. Regarding the functional result of the intervention measured with the modified Rankin Scale (mRS) at discharge (**Figure 1**), it is noteworthy that 27.3% of the patients were discharged without disability (mRS = 0–1). For

Characteristics	**Patients**
	N = 231
Age (average ± SD[a])	67.1 ± 13.1
≥ 65 years (%)	143 (61.9%)
Male gender (%)	136 (58.9)
Mapuche ethnicity (%)	20 (8.7)
Discharge mRS 0–1[b] (%)	42 (26.1%)
Discharge mRS 0–3[b] (%)	76 (47.2%)
Start-to-door time (median, IQR[c])	105 (70.5–156.5)
Door-to-needle time (median, IQR[c])	71 (53–102)
Start-to-needle time (median, IQR[c])	185 (136–235)
Door-to-needle time ≤ 60 min (%)	79 (34.2)
Start-to-needle time ≤ 180 min (%)	110 (47.6%)

[a]Standard deviation.
[b]modified Rankin Scale.
[c]Interquartile range.

Table 2. Clinical characteristics of thrombolysed patients.

Year	N	Rate IVT[a] (%)	Median SDT[b] (minutes)	Median DNT[c] (minutes)	Median SNT[d] (minutes)	% DNT ≤ 60 min
2012	5	0.7	24	85	154	0
2013	11	1.2	93	111	200	36.4
2014	24	2	79	97	180.5	8.3
2015	44	3.6	91	71	182.5	43.2
2016	65	5.4	132.5	71.5	207	27.7
2017	58	4.8	104	57	156.5	44.8
2018	24	5.5	153	56	163	41.7
Total	231	3.2	105	71	185	34.2

[a]Intravenous thrombolysis.

[b]Start-to-door time.

[c]Door-to-needle time.

[d]Start-to-needle time.

Table 3. Evolution of the thrombolysis rate, time parameters, and percentage of patients who received thrombolysis in ≤60 min.

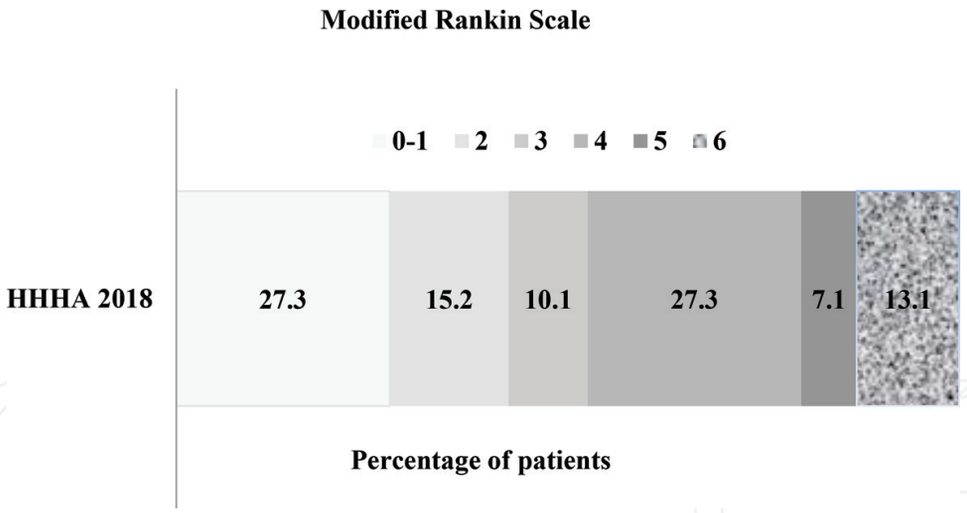

Figure 1. Evaluation of disability at discharge in patients with acute ischemic stroke who received intravenous thrombolysis [14].

this subgroup of patients (N = 106), the median of the NIHSS scale at discharge was 5 points (IQR 1–14). The mortality rate was 13.1%. In relation to the causes of death, in seven patients, it was due to the AIS. Two cases were due to symptomatic hemorrhagic transformation and four patients due to complications not related to the AIS: bronchial cancer, cutaneous focus sepsis, pulmonary focus sepsis, and severe pneumonia. In addition, 13 patients with hemorrhagic transformation (12.3%) were registered, of whom 6 (5.7%) were symptomatic. Four patients

developed an intrahospital AIS, with a 66-year-old man who suffered cerebral infarction after a coronary angiography. On the other hand, IVT plus mechanical thrombectomy was performed in four patients. In this subgroup, a 51-year-old patient died as a result of a malignant infarction of the right middle cerebral artery due to an occlusive carotid dissection [14].

In our hospital 1200, AIS is diagnosed per year approximately. Therefore, the rate of thrombolysis increased from 0.7% in 2012 to 5.5% in 2018. **Table 3** shows the evolution of the number of patients treated per year, the DNT, and the percentage of subjects treated who were thrombolysed within 60 min.

6. Discussion

Intravenous thrombolysis in AIS is feasible to be performed in public hospitals, and particularly in regions of our country. In our series, the median DNT was 71 min. The possible causes for the result of this indicator are: emergency service collapsed, delay in prioritization, delay in the evaluation by neurologist, delay in the taking of neuroimaging, lack of space in the resuscitation box, waiting for the result of exams (INR), etc. In our series, it was not possible to assess the disability of the subjects at 3 months. In this sense, early outcome evaluations have been used, such as the score on the NIHSS scale on the second and seventh day of evolution of the AIS, which have been shown to predict, with adequate accuracy, the functional results at 3 months [24, 25]. In our study, the median of the NIHSS score at discharge was 4 points, with a prethrombolysis score of 13 points (**Figure 2**). The greater severity of the AIS, compared with

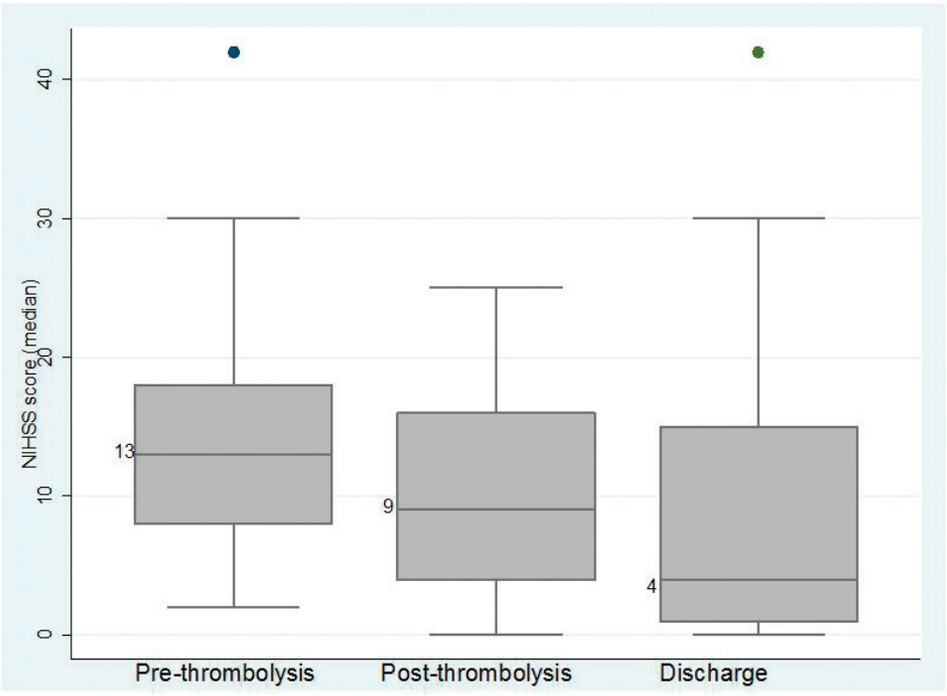

Figure 2. Evolution of the NIHSS score in 231 patients with acute ischemic stroke treated with intravenous thrombolysis.

other series, could be explained by the high percentage of TACI infarcts and cardioembolic AIS. The 5.7% of symptomatic intracerebral hemorrhages (sICH) observed in our series are comparable to that reported in national and foreign studies. For example, a recent meta-analysis of 12 randomized clinical trials of IVT up to 6 h from the onset of symptoms, which included 7012 patients, reported an ICH rate of 7.7%, with a fatal ICH rate during the first 7 days of 3.6%, and a mortality of 8.9% within 7 days, and of 19.1% until the end of the follow-up period [26]. When presenting our results, we must emphasize that the HHHA does not have a specific infrastructure to attend to neurological patients, that is, a stroke unit. These units have demonstrated their cost-effectiveness in decreasing mortality and disability due to stroke [27]. In our reality, not all thrombolysed patients access the intensive care unit and complete 24–48 h of observation in the emergency service, being later hospitalized in the internal medicine service.

The developing world carries the highest burden of stroke mortality and stroke-related disability. The number of stroke patients receiving alteplase (r-tPA) in the developing world is extremely low. Prehospital delay, financial constraints, and lack of infrastructure are main barriers of thrombolysis therapy in developing countries [28]. Stroke thrombolysis is currently used in few developing countries like Brazil, Argentina, Chile, Senegal, Iran, Pakistan, China, Thailand, and India. Most of the centers with the infrastructure to deliver thrombolysis for stroke are predominantly private sector, and only available in urban areas [29].

The rate of thrombolysis that started with 0.7% for the period May-December 2012 rose to 5.5% in the period January-April 2016 (**Table 3**). For this change, we consider that the presence of the neurologist, since July 2013, in the emergency service in the 24/7 modality has been fundamental.

Our thrombolysis rate is comparable with that observed in other Chilean public hospitals, but it is very low compared to national private clinics that have reported a rate greater than 10% [5]. According to our records, 19.1% of patients with AIS consult within 3 h of the start of symptoms, with a median of approximately 10 h, until the consultation. We believe that with educational campaigns aimed at the community, and the socialization of our IVT protocol to the hospitals and health centers of the Araucanía region, we can increase the rate of thrombolysis in the medium term. The thrombolysed patients had a shorter duration of hospitalization (median of 8 days), considering that the average stay of patients who do not receive IVT has been estimated between 14 and 15 days in other public hospitals [30, 31]. Our results, which constitute the largest reported series of IVT in AIS, in Chilean public hospitals, fill us with satisfaction and optimism. They are also an enormous incentive to continue increasing the number of patients treated and continue to improve the quality of care.

7. Future of the acute management of ischemic stroke in the Araucanía region

About 80% of the population in Chile is treated in the public health system. On the other hand, it is expected that the incidence of stroke will increase significantly in our country due to the aging of the population. This is why we see the need to set a reperfusion protocol for acute ischemic stroke in the 24/7 modality that includes intravenous thrombolysis and mechanical

thrombectomy in selected cases. On the other hand, node hospitals in the region are expected to have a scanner in the medium term, which would allow telethrombolysis. We also consider the need to have a stroke unit and/or a neurological intermediate unit in our hospital for the adequate management of patients with acute stroke. In short, we hope that the HHHA will become a comprehensive stroke center.

8. Conclusion

Intravenous thrombolysis in acute ischemic stroke is feasible to be performed in public hospitals, and particularly in regions of our country. The presence of neurologists 24/7 in the Emergency Department has allowed us to increase the quantity and quality of IVT in our hospital, measured by thrombolysis rate and by process indicators such as door-to-needle time.

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Conflict of interest

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