

In-Hospital Acute Ischemic Stroke is Associated with Worse Outcome: Experience of a Single Center in Santiago Chile

Alejandro Brunser, MD,* Victor Navia V, MD,†¶ Patricia Araneda, MD,‡¶
Enrico Mazzon, MD,†¶ Paula Muñoz, MD, PhD,†¶ Gabriel Cavada, PhD,§
Verónica V. Olavarría, MD, MSc,¶ and Pablo M. Lavados, MD, MPH†¶

Objectives: In-hospital acute ischemic stroke (HIS) accounts for 2–17% of all acute ischemic strokes (AIS) seen in hospital and they have worse prognosis. In this study we aimed to identify the frequency of HIS and their characteristics in our center. **Materials and Methods:** Retrospective analysis of a prospective register of patients with AIS seen at Clínica Alemana de Santiago, between January 2017 and January 2019. HIS and community onset ischemic strokes patients (CIS) were compared, univariate analysis was performed, covariates with $p < 0.25$ were selected for multivariate analysis. Differences between, proportion of strokes treated with thrombolytic therapy, door to needle time were compared between HIS and CIS patients, as also mortality rates at 90 days. **Results:** During the study period 369 patients with AIS were seen; of these 20 (5.4%, 95 CI%, 3.5–8.2) corresponded to HIS. In univariate analysis, HIS compared to patients arriving from the community to the emergency room, suffered more frequently from, heart failure ($p = 0.04$), and active malignancies ($p < 0.001$). HIS patients had longer times from symptom onset to non-contrast brain tomography (540 ± 150 minutes); they were also less frequently treated with intravenous thrombolysis compared to community AIS: 15% versus 30% respectively ($p = 0.08$). Mortality rates at 90 days were higher in HIS: 30 versus 5% ($p = 0.001$). **Conclusions:** In this cohort, HIS patients suffered delays in their neuroimaging studies and received less intravenous thrombolysis; this underscores the need for a standardized approach to the recognition and management of in-hospital acute ischemic stroke.

Key Words: Stroke—In-hospital onset stroke—Stroke and cerebrovascular—Outcome

© 2021 Elsevier Inc. All rights reserved.

Introduction

Between 2.2 to 17% of all cases of acute ischemic stroke (AIS) have their symptom onset while hospitalized for

another cause. This group of patients suffering in-hospital acute ischemic strokes (HIS) represents a unique population with different risk factors, delays in diagnosis, higher

From the *Departamento de Urgencia y Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile; †Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Chile; ‡Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Chile; §Unidad de Investigación y Ensayos Clínicos, Departamento de Desarrollo Académico e Investigación, Clínica Alemana de Santiago, Facultad de Medicina Universidad Finis Terrae, Chile; and ¶Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría y Departamento de Paciente Crítico, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile.

Received February 24, 2021; revision received May 5, 2021; accepted May 8, 2021.

Research conducted at: Clínica Alemana de Santiago.

Corresponding author. E-mail: abrunser@alemana.cl.

1052-3057/\$ - see front matter

© 2021 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105894>

NIHSS, low treatment rates of intravenous thrombolytic therapy and worse outcomes when compared to those who arrive to an emergency room (ER) with community onset ischemic strokes (CIS).^{1–5}

The aim of this study was to identify the frequency of HIS and compared their management to CIS patients in our center.

Methods

In this retrospective analysis of a prospective registry, we included all patients with AIS seen between January 2017 and January 2019 at Clínica Alemana de Santiago. Since 2008 in AIS cases arriving to the ER, a stroke code is activated and neuroimaging plus laboratory exams are ordered by the staff and they are evaluated immediately by the neurologist on call, according to a standardized protocol which has been described previously.⁶ For patients who had a stroke during their stay in an intensive, intermediate or cardiological units, the physician on call in the unit contacts directly the stroke team on call, or the ER neurologist during night shift. Finally, for those patients who suffer a stroke in the medical clinical ward, an emergency code (2424), is activated by any member of the patient's care-team (nurse, physical therapist, resident, etc.). The Code is a general hospital wide alarm that means that a patient suffering a severe condition in the hospital ward (seizure, stroke, cardiac arrest, fall or other emergencies). It directs a team formed by 2 emergency physicians and 1 emergency nurse to the floor where the emergency happened, in a case of a stroke, the emergency doctor after evaluating the patient calls directly the stroke team.

For AIS occurring in a special unit or medical ward, the clinical, imaging evaluations and treatment decisions were the same as those seen of the patients seen at the ER, but are ordered after clinical evaluation.

For HIS patients, time from probable symptom onset to NCCT was recorded as the door to needle time, which was considered the time between the probable symptom onset and the thrombolytic bolus.

In-hospital transient ischemic attacks (TIAs), brain hemorrhages and stroke mimics were excluded from this analysis.

Functional outcomes were assessed with the modified Rankin Scale (mRS), by the treating physician at discharge and at 90 days by a structured telephone follow-up.

The Ethics Committee of Universidad del Desarrollo, Clínica Alemana de Santiago approved the registry protocol, and patients or their relatives provided written informed consent.

Statistical analysis

Continuous variables were described using means and standard deviations while categorical variables were described using frequencies and proportions. HIS and CIS

patients were compared and univariate screening was performed with t-test for continuous variables and Chi-square for categorical variables; covariates with $p < 0.25$ were selected for multivariate analysis according to Hosmer-Lemeshow criteria. This value was used instead of the more classic $p < 0.05$, because this latter often fails to identify variables known to be important and in addition it has the disadvantage of including variables that could be of questionable importance. Differences between outcomes (proportion of strokes treated with intravenous thrombolysis TT or thrombectomy, door to needle time in those receiving TT) were compared between HIS and CIS patients, as also the mRS at discharge and at 3 months. A multivariable analysis was carried out and variables with a significance level of 5% were considered significant. All data analyses were performed using STATA version 16.0.

Results

A total of 369 patients with AIS were seen at Clínica Alemana de Santiago between January 2017 and January 2019, of whom 20 (5.4%, 95 CI%, 3.5–8.2) corresponded to HIS while 349 cases arrived to the ER.

HIS patients suffered their AIS as inpatients in the cardiology care unit in 8 cases, in other intensive care units in 2 cases, in the oncological ward in 4 patients, and in other, lower complexity medical wards in 6 cases.

HIS patients were hospitalized for the following diagnosis: acute ischemic heart disease (5 cases), cancer diagnosis, treatment or complications (4 patients), metabolic encephalopathy's (3 cases), heart surgery and cardiac arrhythmias (2 cases each), aortic dissection (1 case), vertebral dissection 1 case and finally one case of pulmonary embolism.

HIS patients had similar rates of independent functional status before admission compared to CIS patients, but they presented more frequently conditions such as heart failure ($p=0.04$), and active malignancies ($p < 0.001$), when compared to CIS patients (Table 1).

The mean and median NIHSS scores on admission for HIS and CIS patients were similar; $8.2 \pm 7.9 / 5$ and $6.2 \pm 7.6 / 3$, respectively.

HIS patients showed a significant time lag until neuroimaging investigations were performed, with 540 ± 150 minutes from the probable beginning of symptoms to NCCT. This group also receives less frequently TT than CIS patients (15% versus 30% ($p = 0.08$)) and demonstrated a trend to longer door-to-needle times (88 ± 60 versus 44.9 ± 27.5 ($p = 0.17$)). (Table 2) Only 1 HIS patient was treated with mechanical thrombectomy, within 130 minutes of symptoms onset to groin puncture time.

HIS cases had higher mortality than CIS patients at 90 days (30% versus 5% ($p=0.001$)), and their mRS at discharge and at three months was higher when compared to CIS patients (Table 3).

Table 1. Baseline characteristics of patients with in-hospital vs community-onset stroke, and univariate analysis correlating clinical variables between them.

Variables	HIS [†] N= 20 (5.4%)	CIS [‡] N= 349 (94.6%)	P
Mean age, years (SD)	68.4 (±17.9)	65.8 (±15.9)	0.65
Women (%)	10 (50)	156 (44.6)	0.65
Previous Rankin			0.51
Mean	0.8 ±1.47	0.6 ±1.2	
Median	0	0	
Hypertension	12 (60%)	216 (61.8)	12 (60)
Diabetes mellitus (%)	54 (15.4)	4 (20)	0.53
Hypercholesterolemia (%)	105 (30.8)	9 (45)	0.21
Tobacco (%)	166 (48)	12 (60)	0.255
Heart Failure (%)	99 (28.3)	10 (50)	0.04
Atrial fibrillation (%)	36 (10.3)	3 (15)	0.2
Previous stroke	70 (20)	3 (15)	0.7
Active tumors	38 (10.7)	7 (35)	< 0.001
First NIHSS [§]			0.27
Mean	8.2±7.9	6.2±7.6	
Median	5	3	
Time from symptoms to TC , minutes mean ± SD	540 (±150)	800 (±234)	0.7
Lacunar Stroke	1(5)	39 (11.1)	0.7

[†]In-hospital acute ischemic stroke.

[‡]Community onset ischemic strokes.

[§]National Institutes of Health Stroke Scale.

^{||}Non-contrast brain Computed Tomography

Table 2. Care and outcomes of patients with in-hospital vs community-onset stroke.

Variables	HIS [†] N= 20 (5.4%)	CIS [‡] N= 349 (94.6%)	P
Thrombolytic treatment	3 (15)	123 (35.2%)	0.08
Door to needle time (mean minutes SD)	88 (±60)	44.9 (±27.5)	0.17
Mechanical Thrombectomy	1 (5)	29 (8.3)	0.9
Discharge NIHSS [§]	1.57± 2.1	2.38±4.5	0.5
Discharge mRS			0.03
Mean	2.65 ±2.1	1.75 ±1.75	
Median	3	1	
Mortality at discharge	6 (30)	18 (5.1)	0.001
mRS at 90 days			0.03
Mean	2.3 ±2.4	1.72 ±1.93	
Median	2	1	
Discharge NIHSS	1.57± 2.1	2.38±4.5	0.5
Discharge mRS			0.03
Mean	2.65 ±2.1	1.75 ±1.75	
Median	3	1	
Mortality at discharge	6 (30)	18 (5.1)	0.001
mRS at 90 days			0.03
Mean	2.3 ±2.4	1.72 ±1.93	
Median	2	1	

[†]In-hospital acute ischemic stroke.

[‡]Community onset ischemic strokes.

[§]National Institutes of Health Stroke Scale.

^{||}modified Rankin Scale score.

In the multivariate analysis HIS patients showed higher rates of heart failure (OR: 2.52, 95% CI 1.01–6.25) and active malignancies (OR: 4.4, 95% CI 1.65–11.7) compared to CIS. Additionally HIS patients had higher mortality

rates at 90 days (OR: 7.26, 95% CI 2.49–21.1) and a trend for less TT.

HIS patients who were treated with thrombolytic drugs had significantly lower NIHSS scores at 90 days

Table 3. Variables independently associated with in-hospital acute ischemic stroke compared to community onset ischemic strokes in the multivariable analysis.

Variable	OR	95% CI	P Value
Cardiopathy	2.52	1.01–6.25	0.04
Active malignancies	4.4	1.65–11.7	0.003
Intravenous thrombolysis	0.32	0.09–1.1	0.07
Mortality at 90 days	7.2	2.49–21	< 0.001

($p < 0.001$) and a better outcomes when measured by mRS at 3 months ($p = 0.07$) when compared to those HIS patients not treated with intravenous thrombolytic drugs.

Discussion

Among all AIS seen at our center during a period of 2 years, HIS patients represented almost 1 in 20 cases (5%), which is consistent with those of other experiences that describe frequencies between 2.2 and 17%.^{1–5}

We found that HIS patients have different comorbidities compared to CIS cases, with a higher prevalence of heart failure and active malignancies that could cause a hypercoagulable state, similar to what has been described previously.^{1,4,7–9} The most common medical service caring for patients who suffer HIS was the cardiologic care unit in agreement with the study of Park et al.¹² In some institutions cardiology-related departments demonstrated a 10-fold higher frequency of strokes.⁸

As previously described, our HIS patients did not experience more severe strokes compared to CIS patients, (1) a finding that could be related to the small number of HIS patients in this series.

HIS patients had long times from symptom onset to NCCT, being similar to the 600 minutes described by Kassardjian et al.¹⁰ This is surprising considering that in many institutions, like in ours, these patients are closely monitored, have available rapid access to laboratory tests and to brain imaging, stroke neurologists and therapeutic interventions. This longer interval decreases their chances of being treated with thrombolytic drugs or their use being effective; in our cases only 3 HIS patients (15%) were treated with TT, a finding that is similar to the 2.6% to 11% described previously.^{2,8,11} We also found longer door-to-needle times in these few patients treated with TT. This contrasts dramatically with patients first seen at the ER, where door to needle time was 44.9 ± 27.5 , and not infrequently treated in less than 20 minutes.¹² It is possible that this is associated to the fact that only 1 in-hospital AIS patient is seen per month and also that 1 thrombolytic treatment is carried out every 8 months, added to the fact that in our center code 2424 is a

general alarm code generated equally for a patient falling or a patient with a suspected stroke, resulting in nurses, physical therapist and floor residents less familiar and trained in stroke care, and less capable to recognize stroke symptoms. Educational training in stroke recognition and a specific stroke emergency code that rapidly activates a specialized stroke or neurological teams and mobilizes appropriate resources have demonstrated to reduce door to needle time in HIS patients,¹⁰ also stocking of alteplase on additional floors as well as education and hands-on alteplase reconstitution simulations for resident physicians has demonstrated to reduce the time of stroke alert to needle in HIS patients.¹³ Similar hospital delays in thrombolytic treatment also have been observed for myocardial infarction in the in-hospital environment compared to those occurring in the community.⁴

HIS portends a serious prognosis, with a mortality rate 5 times greater than those of community-onset strokes and absolute in-hospital mortality rates of 30%. This is probably due to the concomitant presence of other conditions with bad prognosis like active cancer or severe cardiopathies, and less revascularization treatments.⁴ All these factors could be associated with HIS presenting worse outcomes at 90 days.

Our HIS patients that were treated with thrombolytics demonstrated equivalent rates of neurologic improvement compared to community-onset strokes as shown in a retrospective review.¹⁴

The application of inpatient code stroke algorithms and educational interventions have been shown to improve the prompt management of inpatient strokes, reducing times from eventual symptoms beginning to NCCT by 440 min.¹⁰

The present study has several limitations. The main one is that we did not include information on the reasons for the delays in the diagnosis or TT treatment. Furthermore, inpatients represent a rather small sample of patients not allowing statistical adjustments for age, NIHSS or stroke type. Finally, we did not include false codes that finally corresponded to stroke mimics in this analysis, which could represent a number as high as 67% of all in-hospital stroke alerts¹⁵ and we did not assess stroke recurrence or their causes of death. The main strengths of our study are that it was conducted consecutively in a clinical setting in patients with AIS, in a comprehensive stroke centre with important levels of experience in thrombolytic treatment.

Conclusions: Our study shows that in-hospital stroke onset was uncommon. They are less likely to receive timely imaging studies and recanalization/reperfusion treatments and have worse outcomes compared to those patients admitted through the ER. Organizational and educational interventions are needed to improve the management of inpatient strokes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

None

Potential financial interests of the authors: Alejandro M Brunser: reports Grant from Clínica Alemana de Santiago Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, and CONICYT, Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) Regular 1181238 during the conduct of the study.

Victor Navia: reports no conflicts of interest

Patricia Araneda: reports no conflicts of interest

Enrique Mazzon: reports no conflicts of interest

Paula Muñoz: reports research grant from Clínica Alemana de Santiago and from CONICYT Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) Regular 1181238 during the conduct of the study

Gabriel Cavada: reports no conflicts of interest

Verónica Olavarria: reports receiving research grant from Clínica Alemana de Santiago and Boehringer-Ingelheim for the RECCA study and a research grant from ANID-FONDECYT outside the submitted study.

Pablo M. Lavados reports, grants from Clínica Alemana de Santiago and financial support from Boehringer-Ingelheim for the RECCA registry, grants from ANID-FONDECYT, grants from The George Institute for Global Health outside the submitted work.

References

1. Kimura K, Minematsu K, Yamaguchi T. Characteristics of in-hospital onset ischemic stroke. *Eur Neurol* 2006;55(3):155-159.
2. Cumbler E, Murphy P, Jones WJ et al. Quality of care for in-hospital stroke: analysis of a statewide registry. *Stroke* 2011;42:207-210.
3. Silver FL. In-hospital stroke: the neglected group. Paper presented at: 4th Annual Summit of the North-East Cerebrovascular Consortium; 2009; Boston, MA.
4. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get with the Guidelines-Stroke. *Stroke* 2014;45:231-238.
5. Dulli D, Samaniego EA. Inpatient and community ischemic strokes in a university hospital. *Neuroepidemiology* 2007;28:86-92.
6. Brunser AM, Lavados PM, Cárcamo DA, et al. Additional information given to a multimodal imaging stroke protocol by transcranial Doppler ultrasound in the emergency room: a prospective observational study. *Cerebrovasc Dis* 2010;30:260-266.
7. Iguchi Y, Kimura K, Kobayashi K, et al. In-hospital onset ischemic stroke may be associated with atrial fibrillation and right-to-left shunt. *J Neurol Sci* 2007;254:39-43.
8. Park JH, Cho HJ, Kim DW, Lee DW, Choi HY, Kim SM, et al. Comparison of the characteristics for in-hospital and out-of-hospital ischaemic strokes. *Eur J Neur* 2009;16:582-588.
9. Vera R, Lago A, Fuentes B, et al. In-hospital stroke: a multi-center prospective registry. *Eur J Neurol* 2011;18:170-176.
10. Kassardjian CD, Willems JD, Skrabka K, et al. In-patient code stroke. a quality improvement strategy to overcome knowledge-to-action gaps in response time. *Stroke* 2017;48:2176-2183.
11. Farooq MU, Reeves MJ, Gargano J, et al. for the Paul Coverdale National Acute Stroke Registry Michigan Prototype Investigators. In-hospital stroke in a statewide stroke registry. *Cerebrovasc Dis* 2008;25:12-20.
12. Brunser AM, Mazzon E, Muñoz P, et al. Determinantes del tiempo puerta-aguja en trombolisis endovenosa en el infarto cerebral, experiencia de un centro [determinants of door to needle time for intravenous thrombolysis in acute ischemic stroke]. *Rev Med Chil* 2020;148:1090-1095.
13. Pines AR, Das DM, Bhatt SK, et al. Identifying and addressing barriers to systemic thrombolysis for acute ischemic stroke in the inpatient setting: a quality improvement initiative. *Mayo Clin Proc Innov Qual Outcomes* 2020;6:657-666.
14. Masjuan J, Simal P, Fuentes B, et al. In-hospital stroke treated with intravenous tissue plasminogen activator. *Stroke* 2008;39:2614-2616.
15. Cumbler E, Simpson J. Code stroke: multi-center experience with in-hospital stroke alerts. *J Hosp Med* 2015;10:179-183.