Prognosis of aphasia in stroke patients early after iv thrombolysis.

Kremer, Christine; Perren, Fabienne; Kappelin, Johan; Selariu, Eufrozina; Abul-Kasim, Kasim

Published in:
Clinical Neurology and Neurosurgery

DOI:
10.1016/j.clineuro.2012.05.019

2013

Prognosis of Aphasia in Stroke Patients early after iv Thrombolysis

Christine Kremer, MD[a], Fabienne Perren, MD[c], Johan Kappelin[a], Eufrozina Selariu[b], MD, Kasim Abul-Kasim, MD PhD[b]

[a]Department of Neurology, Skåne University Hospital - Malmö, Lund University, Sweden
[b]Diagnostic Centre for Imaging and Functional Medicine, Skåne University Hospital – Malmö, Lund University, Sweden
[c]Department of Neurology, University Hospital and Medical Faculty, University of Geneva, Switzerland

Running title Prognosis of aphasia after thrombolysis

Keywords: thrombolysis - stroke- aphasia-outcome

Address of correspondence:
Christine Kremer, MD
Department of Neurology
Skåne University Hospital-Malmö
Lund University
Ing. 53
SE-20502 Malmö
Tel: 0046(0)40336945
Fax:0046(0)40333055
christine.kremer@skane.se

ABSTRACT

Objective – Intravenous rt-PA (iv) thrombolysis is given more deliberately to stroke patients presenting with aphasia. Early outcome data is lacking. Aim of this study was to determine early benefit from rt-PA in patients with aphasia. *Methods* – Data of stroke patients treated by iv thrombolysis 2002-2008 was scrutinized for the presence of aphasia defined as ≥1 point for aphasia on the National Institute of Health Stroke Scale (NIHSS). Improvement was defined as a gain of ≥1 point within 24 hours. Cranial computed tomography (CT) scans were evaluated regarding early ischemic changes (EICs), infarct volume and localization *Results* – 50 patients with aphasia were included. 16 (32%) of patients improved (4 (36%) minor, 7 (41%) moderate, 5 (23%) major stroke patients), while 44 (62 %) remained unchanged. Of 28 patients with EICs, 10 (36 %) improved compared to 7 out of 22 (32%) patients without (p=0.773). Aphasia outcome was significantly associated with infarct volume at admission and at 24 hours (Kruskal Wallis, p=0.033, p=<0,001, respectively). *Conclusion* – EICs are not predictive of aphasia outcome and patients with improvement showed smaller infarct volumes. 32% improved in their aphasia within 24 hours, probably due to early reperfusion, while 62% remained unchanged. This might justify a closer follow-up of aphasia in stroke patients at the acute stage.

Introduction

Aphasia is diagnosed in 21-38 % [1-4] of admitted stroke patients at the acute stage. Patients with aphasia often remain disabled despite low baseline NIHSS scores [5]. These patients are increasingly treated with thrombolysis. Retrospective studies showed that patients with mild stroke symptoms and low baseline NIHSS scores may benefit from thrombolysis with low complication rates [6,7]. On the other hand could it be shown that spontaneous recovery of aphasia as measured by NIHSS occurred in 74% of all and 90 % of patients with mild stroke

symptoms after six months [8]. Data regarding outcome of aphasia in the 24 hours window is lacking.

Aim of this observational study was to find out which early clinical benefit can be expected in patients with aphasia receiving iv thrombolysis. Secondly parameter predictive of aphasia outcome were evaluated.

Materials and Methods

Medical records of prospectively collected data of stroke patients treated by iv thrombolysis (0,9 mg rtPA/kg of body weight infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus dose over 1 minute, maximal dose 90 mg) in the three hours window during a six years period were retrospectively analysed. All patients had common stroke work-up, assessment of stroke risk factors, Carotid ultrasound, 24 hour ECG monitoring and, in most cases transthoracic echocardiography; some patients had transesophageal echocardiography.

Patients with aphasia (scoring at least one point for aphasia on the 3 points scale; 1 point: mild to moderate aphasia, 2 points: severe aphasia, 3 points: mute or global aphasia) according to the initial assessment made before thrombolysis were included in the analyses of this study. Patients with incomplete NIHSS charts were excluded. Patients who, in the absence of language improvement, after evaluation by a speech therapist had been considered not to be suffering from aphasia were also excluded. Baseline and demographic data was extracted from the local databank (Malmö).

Common risk factors of stroke were analysed and stroke aetiology was classified according to the TOAST classification [9] by an experienced neurologist. Development of neurological symptoms in the selected patients was assessed using the NIHSS-charts. For aphasia, a change of ≥ 1 point was considered as a significant change in aphasia outcome. Significant change in global neurological symptoms (aphasia excluded) was defined as a total resolution of the

neurological deficit or a change of ≥ 4 points. Stroke severity according to NIHHS was subdivided in minor stroke (≤ 7 points), moderate stroke (8-15 points) and major stroke (≥ 16 points). Long-term outcome was evaluated by clinical examination at three months by the modified Rankin scale (mRS).

All patients were examined with a baseline nonenhanced CT and nonenhanced CT 24 hours after treatment, using a multislice CT (SOMATOM Sensation 16, Siemens AG, Forchheim, Germany). The baseline CTs were evaluated by two specialists in Neuroradiology at two different occasions without knowledge of symptoms or the side affected. Images were evaluated regarding the occurrence of early ischemic changes (EICs). In cases of disagreement a joint evaluation by the two readers was performed to reach a consensus about the occurrence of EICs. Measurement of infarct volume was performed on CT 24 hours after treatment using the "Volume" application at a Leonardo workstation (Siemens AG, Medical Solutions, Erlangen, Germany). The volume of every individual infarct was given in cm^3.

Statistical analyses were performed using SPSS 17. For descriptive purposes means ± SD, median, and percentages were presented. Mann-Whitney or Kruskal Wallis test was used when comparing categorical data with continuous data while Pearson Chi-Square was used when comparing two categorical variables. The statistical significance was set to a p-value <0.05.

Results

During the period 2002-2008, 172 patients were treated by iv thrombolysis. Fifty patients with aphasia according to NIHSS were included in the study. 31 patients were evaluated by a speech therapist. Six patients were excluded because of misdiagnosis and two because the thrombolytic therapy was not completed.

11 (22%) patients had suffered a minor stroke, 17 (34%) patients a moderate stroke and 22 (44%) patients a major stroke. The percentage of patients with atrial fibrillation (AF) (44%) and cardioembolic stroke (52%) was high in our study population, other clinical and demographic data see Table 1.

The incidence of AF (38% (6/16 pts.) vs. 47% (16/34 pts.)) and cardioembolic stroke (50% (8/16 pts.) vs. 52% (18/34 pts.) was similar in patients who improved vs. those who were unchanged or impaired in their aphasia.

Course of aphasia and global neurological stroke symptoms 24 hours after thrombolysis is shown in Table 2. At 24 hours, 16 patients (32 %) were improved in their aphasia compared to 23 patients (46 %) with improvement in the global neurological symptoms. This difference was not statistically significant (Chi-square test, p=0,22). Five patients suffered an intracranial hemorrhage/hemorrhagic transformation within 24 hours after thrombolysis. Three were asymptomatic; two symptomatic (increase of $\geq$ 4 points NIHSS).

There was statistically significant correlation between the aphasia score at 24 hours and NIHSS at admission (Pearson correlation, r=0.427, p=0.002). Patients with complete resolution of aphasia had NIHSS of 3.6±2.6 compared to 9.4±6.4, 13.2±6, and 20±6 among patients with aphasia score 1, 2 and 3, respectively.

Out of 28 patients (56 %) who showed EICs on baseline CT, 18 (64 %) deteriorated or were unchanged in their aphasia after 24 hours. Out of 22 patients (44 %) with no EICs, 15 (68 %) deteriorated or were unchanged (Chi-square test , p=0.773), see Table 3.

There was statistically significant association between infarct volume and the aphasia score at admission, and at 24 hours after thrombolysis (Kruskal Wallis test, p=0.033, 0.001, and <0.001, respectively). Patients with no aphasia 24 hours after thrombolysis showed an infarct volume of 0.5±1 cm^3 compared with 106±87 cm^3 among patients with aphasia score of 3, Table 4.

There was also statistically significant correlation between mRS and the aphasia score at 24 hours after thrombolysis (Kruskal Wallis test, p=0.005) but not with aphasia score at admission (Kruskal Wallis test, p=0.225). Patients with no aphasia at 24 hours after thrombolysis had mRS of 1.1±1.7 compared with 4.4±1.8 among patients with aphasia score of 3, see Table 4 and Figure 1.

There was no statistically significant correlation between the aphasia score at 24 hours after thrombolysis and the age (r=-0.024, p=0.871), gender (Chi-square test, p=0.903), or death at three months (Chi-square test, p=0.235).

Discussion

In our study one third of patients with aphasia improved, while two thirds remained unchanged within 24 hours after iv thrombolysis. Aphasia at 24 hours was correlated to a higher morbidity according to the mRS at three months. In a recent study it could be shown that the course of aphasia might be benign in patients with mild strokes showing an overall improvement of 86%, and a recovery rate up to 90% as measured by NIHSS after six months questioning the net benefit of thrombolysis in these cases. Twenty-eight patients could be followed-up after a mean of five days, and 26 after 6 months with improvement in 86% and resolution in 80% of all cases. Aphasia outcome at the early stage was not given. At 6 months only the pre-stroke mRS score was associated with improvement of aphasia [10]. The short follow-up of our study population can explain the lower improvement rates. Long-term improvement of aphasia is dependant on neuronal reorganisation, pre-morbid mRS score, and speech therapy. As shown by Inatomi et al. the NIHSS is significantly correlated with the presence of aphasia on admission. 46% of the patients improved after 10 days in a cohort of 855 stroke patients of whom a minority received thrombolysis [11]. Atrial fibrillation was

present in nearly half of our patients and cardioembolism the most common stroke aetiology, this was previously shown in aphasic patients [11].

Eleven patients were admitted with a score of = 7 NIHSS. Patients with aphasia show often low baseline NIHSS scores and the proportion of patients with stroke mimics is higher [12]. This could lead to an eventual exclusion of patients with aphasia supposed to recover more likely. A low baseline NIHSS score is not predictive of proximal cerebral artery occlusion which is a poor prognostic parameter [13]. Cho et al. reported two cases of stroke patients with minor aphasia who received successful iv thrombolysis. Both had additional magnetic resonance angiography with diffusion and perfusion weighted imaging showing a significant mismatch and proximal artery occlusion [14].

EICs in patients with aphasia treated with thrombolysis were not a predictor of outcome of aphasia. This is in line with studies showing that EICs in unselected stroke patients receiving thrombolysis did not modify treatment response [15,16]. Studies in selected patients with aphasia are lacking. On the other hand, patients with smaller infarct volumes showed better outcome of aphasia. Infarct volume has been previously shown to correlate with stroke outcome measured according to the mRS at three months among unselected patients treated with thrombolysis [17].

The evaluation of aphasia according to the NIHSS has received critics because of the crude and semi-quantitative character of the scale that allows no distinction of aphasic symptoms (sensory/motor for example). At the same time is it well-standardized and one of the major diagnostic instruments to guide treatment decisions in the acute setting. Due to the lack of a randomized control group the natural course of aphasia in stroke patients with potential spontaneous recoveries could not be determined. Another limitation is the small number of included patients, especially in the subgroups which makes a further analysis difficult.

Conclusions

EICs were no predictor of aphasia outcome in patients receiving iv thrombolysis, and the occurrence of EIC should not lead to withdrawal from iv thrombolysis.

One third of the patients receiving iv thrombolysis improved in their aphasia within 24 hours, while two thirds remained unchanged. Improvement of aphasia can indicate early reperfusion of language areas. Given the low rates of improvement and the high morbidity of patients with aphasia a close follow-up of speech functions at the acute stage is recommended. This would help to identify patients with failed reperfusion and potential benefit of intra-arterial thrombolysis and/or mechanical thrombectomy

References

1 Wade DT, Hewer RL, David RM, Enderby PM.: Aphasia after stroke: natural history and associated deficits. J Neurol Neurosurg Psychiatry 1986; 49: 11-6.

2 Laska AC, Hellblom A, Murray V, Kahan T, von Arbin M. Aphasia in acute stroke and relation to outcome. J Intern Med 2001; 249: 413-22.

3 Kauhanen ML, Korpelainen JT, Hiltunen P, Maatta R, Mononen H, Brusin E, Sotaniemi KA, Myllyla VV: Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. Cerebrovasc Dis 2000; 10: 455-61.

4 Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS: Aphasia in acute stroke: incidence, determinants, and recovery. Ann Neurol 1995; 38: 659-66.

5 Paolucci S, Antonucci G, Pratesi L, Trabellesi M, Lubich S, Grasso MG: Functional outcome in stroke inpatient rehabilitation: predicting no, low and high response patients. Cerebrovasc Dis 1998; 8: 228-34.

6 Engelter ST, Gostynski M,Papa S, Frei M, Born C, Ajdacic-Gross VA, Gutzwiller F, Lyrer PA: Epidemiology of Aphasia attributable to first ischemic stroke: Incidence, severity, etiology, and thrombolysis: Stroke 2006;37:1379-1384

7 Hassan AE, Zacharatos H, Hassandeh B, El-Gengaihy A, Alkawi A, Shhadeh:. Does mild deficit for patients with stroke justify the use of intravenous tissue plasminogen activator? J Stroke Cerebrovasc Dis 2010 Mar;19(2):116-20.

8 Kohrmann M, Nowe T, Huttner HB, Engelhorn T,Struffert T, Kollmar R, Saake M, Doerfler A, Schwab S, Schelling PD: Safety and outcome after thrombolysis in stroke patients with mild symptoms. Cerebrovasc Dis 2009; 27: 160-6

9 HP Adams, Jr, BH Bendixen, LJ Kappelle, J Biller, BB Love, DL Gordon, EE Marsh,3d.KL Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41

10 Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, Kirmani AF, Harris GJ, Koroshetz WJ, Furie KL : The Prognosis for Aphasia in Stroke. J Stroke Cerebrovasc Dis 2010 Dec 23 (Epub ahead)

11 Inatomi Y, Yonehara T, Omiya S, Hashimoto Y, Hirano T, Uchino M.:Aphasia during the acute phase in ischemic stroke. Cerebrovasc Dis 2008; 25: 316-23.

12 Winkler DT, Fluri F, Fuhr P, Wetzel SG, Lyrer PA, Ruegg S, Engelter ST: Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome. Stroke 2009; 40: 1522-5.

13 Maas MB, Furie KL, Lev MH, Ay H, Singhal AB, Greer DH, Gordon JH, Halpern E, Koroshetz WJ, Wade SS: National Institutes of Health Stroke Scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. Stroke 2009; 40: 2988-93.

14 ChoTH, Hermier M, Nighogossian N. Neurological picture: MRI-based thrombolysis in patients with stroke with minor aphasia. J Neurol Neurosurg Psychiatry 2010; 81: 1215-6.

15 Mendizabal JE, Lurie DN, Greiner FG, Shah AK, Zweifler RM: Baseline computed tomography changes and clinical outcome after thrombolysis with recombinant tissue plasminogen activator in acute ischemic stroke. J Neuroimaging 2001; 11: 101-4.

16 Dzialowski I, Hill MD, Coutts SB, Demchuk, AM, Kent DM, Wunderlich O, von Kummer R: Extent of early ischemic changes on computed tomography (CT) before

thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. Stroke 2006; 37: 973-8.

17 Brouns R, Sheoraypanda Y R, Kunnen J, de Surgeloose D, de Deyn PP: Clinical, biochemical and neuroimaging parameters after thrombolytic therapy predict long-term stroke outcome. Eur Neurol 2009; 62: 9-15.

Table 1. Clinical and demographic characteristics of aphasic patients receiving thrombolysis

Number of included patients	50
Men	29 (58%)
Median age (range)	70 (30-90)
Minor stroke	11 (22%)
Moderate stroke	17 (34%)
Major stroke	22 (44%)
Hypertension	24 (48%)
Diabetes	8 (16%)
Hypercholesterolemia	21 (42%)
Current/former smoking	8 (16%)/10 (20%)
Atrial fibrillation	22 (44%)
History of cerebrovascular event	7 (14%)
History of coronary heart disease	10 (20%)
TOAST classification	
Cardioembolic	26 (52%)
Large vessel disease	9 (18%)
Small vessel disease	0
Undetermined	11 (22%)
Others	4 (8%)
Asypymtomatic ICH [a] after thrombolysis	3 (6%)
Symptomatic ICH [b]	2 (4%)

[a] intracranial hemorrhage/hemorrhagic transformation
[b] increase of $\geq$ 4 points NIHSS

Table 2. Global neurological symptoms compared to aphasia 24 hours after thrombolysis.

	Global neurological symptoms			Aphasic symptoms				
	Improved	Unchanged	Deteriorated	Improved	Deteriorated	Unchanged	Total	P -value [a]
Minor stroke	2 (18 %)	7 (64 %)	2 (18 %)	4 (36 %)	6 (55 %)	1 (9 %)	11	0.12
Moderate stroke	10 (59 %)	5 (29 %)	2 (12 %)	7 (41 %)	9 (53 %)	1 (6 %)	17	0.49
Major stroke	11 (50 %)	8 (36 %)	3 (14 %)	5 (23 %)	16 (73 %)	1 (4 %)	22	0.63
Total	23 (46%)	20 (40%)	7 (14%)	16 (32%)	31(62%)	3 (6%)	50	0.22

[a] Improved global neurological symptoms vs. aphasic symptoms. Two tailed Chi –square test.

Table 3. Association between aphasia at 24 hours and different categorical variables.

Aphasia at 24 hours	n	n		P-value
		Gender		
	Female	Male		
Worse or unchanged	13	20		
Better	7	10		0.903
		EICs[a] a at baseline CT		
	No	Yes		
Worse or unchanged	15	18		
Better	7	10		0.773
		Involvement of Broca´s area at baseline CT		
	No	Only Broca´s area	Extensive infarct	
Worse or unchanged	7	8	18	
Better	11	3	3	0.008
		Death at 3 months		
	Survived	Dead		
Worse or unchanged	27	6		
Better	16	1		0.235

[a] EICs: early ischemic changes.

Table 4. Association between aphasia at 24 hours and infarct volume at 24 hours-CT and mRS at three months.

Aphasia scoring	0	1	2	3	P-value
		Infarct volume on 24 hours CT			
At admission		19±26 (5)[a]	49±54 (27)	80±81 (59)	0.033
24 hours after treatment	0.5±1 (0)	22±23 (14)	65±52 (48)	106±87 (66)	< 0.001
		mRS[b] at 3 months			
At admission		2±2.1 (1)	2.6±1.9 (2.5)	3.3±2.1 (3)	0.225
24 hours after treatment	1.1±1.7 (0)	2±2 (1)	2.8±1.6 (3)	4.4±1.8 (5)	0.005

[a] value between parenthesis represent median values.
[b] mRS: Modified Rankin Scale

Figure 1.

Boxplot shows the mRS against different aphasia score at 24 hours after thrombolysis. The grey box shows the upper and the lower bound of the 95 % confidence interval. The black line in the middle of the box indicates the median value while the limits at either end of the longitudinal line indicate the minimal and the maximal values of the mRS.