Original Article

Limitations in thrombolytic therapy in
acute ischemic stroke

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ABSTRACT

Objective: The eligibility for thrombolytic therapy for patients who present to the emergency department with Acute Ischaemic Stroke (AIS) has been researched in this study.

Methodology: Patients who had presented to the emergency department of our hospital between March 2008-2009 and diagnosed as AIS clinically and radiologically were included in the study prospectively.

Results: One hundred and twelve patients were included in the study. Forty nine (43.8 %) were female and the mean age was 68.7± 12.2 (median 71.5). The mean time from the onset of symptom to hospital admission was 12.2±12.9 hours (median 6 hours). Two (1.8%) patients did not have any contraindication for thrombolytic therapy. Arrival time at the hospital of three hours and higher was the single contraindication in 40 (35.7%) patients. The most common four contraindications were delayed admission, multilobar infarct or hypodensity of more than 1/3 of the hemisphere, hypertension and mild neurological symptoms respectively.

Conclusions: Our data suggest that the primary barrier to the delivery of thrombolytic therapy for AIS is delayed arrival of the patient to a hospital, and up to 1/3 of our patients, the percentage arriving within 4 hours of the onset of stroke symptoms, might be eligible for attempted re-perfusion.

KEY WORDS: Stroke, Acute, Thrombolytic therapy.

How to cite this article:

Kocak S, Dogan E, Kokcam M, Girisgin AS, Bodur S. Limitations in thrombolytic therapy in acute ischemic stroke. Pak J Med Sci 2012;28(4):586-590

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*   Received for Publication: January 30, 2012
*   Revision Received: February 3, 2012
*   Final Revision Accepted: June 27, 2012

INTRODUCTION

Following approval by the United States Food and Drug Administration in 1996, the use of thrombolytic therapy for patients with acute ischemic stroke (AIS) has gradually gained wide acceptance all over the world. However, the rate of patients treated with thrombolytic agents has ranged from 3-14%, due to many factors limiting the use of this therapeutic agent.[1-3] Many patients cannot receive intravenous thrombolytic therapy due to a variety of pre-hospital and in-hospital reasons. In this study, the reasons for patients with AIS who could not receive thrombolytic therapy in our hospital have been investigated.

METHODOLOGY

The patients who presented consecutively to our emergency department (ED) with acute ischemic

stroke between March 2008 and March 2009 were included in this study. The study was approved by the local ethical board of our university. Radiological diagnosis was obtained with non-contrasted brain Computed Tomography (CT) and/or Diffusion-weighted Magnetic Resonance Imaging (DWI). All the patients were evaluated by a neurologist and all images were evaluated by a radiologist. The National Institutes of Health Stroke Scale (NIHSS) was used in determining the severity of stroke in the patients.[4] The guideline of the American Heart Association (AHA) which were published in 2007 were taken into consideration for determining the patients for whom thrombolytic therapy was, or was not indicated.[5] The patients who had a hemorrhagic stroke, those who received treatments in other centres and those who did not accept to participate in the study were not included. The arrival time or the pre-hospital delay was defined as the time from the onset of symptom to arrival at the ED. The symptom onset time for patients with wake-up stroke was accepted as last time that the patient was seen as healthy.

There was no interference for routine clinical course of ED during study period. Firstly, a non-contrast enhanced CT is provided in routine practice and then DWI is provided if there is no evidence of ischemia or significant lesion at CT. It was assumed that the patients could be ready for thrombolytic therapy within 30 minutes. That is why the patients who presented to the hospital within the first two and a half hours were considered appropriate for thrombolytic therapy (if no other contraindications were present). Eligibility for rt-PA of the patients who presented to the hospital in the first four hours, were also evaluated separately by considering the results of the new studies where thrombolytic therapy is administered within the first four and a half hours. The patients' demographic and clinical features, arrival time to the ED, stroke severity, radiological findings and contraindications for thrombolytic therapy were recorded. The data obtained were transferred to the SPSS™ 17.0 program of the computer for statistical analysis. The data were summarized as mean± standard deviation, median and percentages. The Chi-square test was used to compare the categorical variables. In the comparison of the numeric data, the T test was used for values with normal distribution, and the Mann-Whitney U test was used to compare ordinal data and values with abnormal distribution. Statistical significance was defined as $p < 0.05$.

RESULTS

Two hundred and thirty nine patients with AIS presented to our department in the study period. However, only one hundred and thirty two patients who were examined by emergency physicians contributing this study during their own shifts were included in the study. Seventeen of them did not give approval to participate in the study. Three patients were also excluded from the study later because of living alone and late awareness of symptoms. Thus, one hundred and twelve of them were evaluated. Forty nine (43.8%) of the remaining 112 patients were female and the mean age was 68.7±12.2 (range, 31-94; median 71.5) (Table-I). However, there was no difference for the mean age between genders (p=0.126). It was reported that stroke symptoms have been noticed after waking up for 21 (18.8%) patients. The mean time from the onset of symptoms to ED arrival was 12.2±12.9 hours (range 1-48 hours, median 6 hours). The details of the arrival times have been explained in Table-I.

Table-I: The demographic and baseline characteristics of the patients with Acute Ischemic Stroke admitted to the Emergency Department.

	n (%)	Mean (median)
Sex		
Female	49 (43.8)	
Male	63 (56.2)	
Age (years)		68.7±12.2 (71.5)
≤65	36 (32)	
>65	76 (68)	
Risk factors		
HT	80 (71.4)	
DM	34 (30.3)	
CHD	34 (30.3)	
AF	30 (26.8)	
Prior stroke	36 (32.1)	
GCS score(baseline)		12.6±3.0 (14)
3-8	16 (14.3)	
9-12	23 (20.5)	
13-15	73 (65.2)	
NIHSS score(baseline)		9.4±7.3 (6.0)
0-6	59 (52.7)	
7-15	32 (28.6)	
16-24	14 (12.5)	
25+	7 (6.2)	
Arrival time (h)		12.2±12.9 (6.0)
≤2.5	17 (15.2)	
≤4	33 (29.5)	
≤6	59 (52.7)	
>6 (max. 48 h)	53 (47.3)	

HT, hypertension; DM, diabetes mellitus; CHD, coronary heart disease; AF, atrial fibrillation; GCS, Glasgow coma scale; NIHSS, National Institutes of Health Stroke Scale.

Sixteen (14%) patients came with private vehicles from the city centre, 16 (14%) were referred from another facility, 28 (25%) came with an ambulance from their homes and 52 (47%) were referred from other counties and boroughs. No difference could be found in terms of arrival times between the patients who came with their own vehicles or those who came with the ambulance, or between those coming from the city centre and the others coming from upstate (p=0.528). Sixty eight (60.7%) patients had more than one chronic-systemic disease (Table-I). No significant difference could be found when the patients having previous stroke and those not were compared for arrival times (p=0.133).

No evidence of ischemia or infarct was found in 61 (64.2%) of 95 (84.8%) patients on whom CT was obtained on ED admission. DWI was provided for these 61 patients except for one patient who was transferred to another facility. Totally, 103 of the 112 patients were provided DWI and radiological findings of acute ischemic stroke were detected in all of them. No difference was found between the arrival times of the patients in whom a lesion was detected in CT and those not detected (p=0.084).

The mean baseline NIHSS score was 9.4±7.3 (median 6.0) and this was significantly higher in patients with hemiparesis or hemiplegia, dysphasia and alterations in consciousness (p<0.000, p=0.013, p=0.003, respectively) (Table-I). Besides, there was a significant positive relation between age and NIHSS scores, a significant negative relation between age and GCS scores (p=0.021, p=0.018, respectively). The baseline NIHSS score was significantly higher in patients who had infarcts of large size or multilobar infarcts (p<0.000). GCS scores were significantly lower (p=0.02). However, no significant relation was found between the arrival time, GCS and NIHSS scores (p=0.632).

When the patients' contraindications for the intravenous thrombolytic therapy were taken into consideration, 50 (44.6%) patients had one contraindication and 60 (53.6%) patients had more than one contraindication. Two (1.8%) patients did not have any contraindication. The only contraindication in 40 of them (35.7%) was the ED arrival in three hours and over. If we accept ED arrival in four hours and under as an appropriate duration for thrombolytic therapy; 55 (49.1%) patients had one contraindication and 52 (46.4%) had more than one. Five patients (4.5%) did not have any contraindication. The number of patients the only contraindication in whom was to have been admitted to our clinic after four hours was 37 (33.0%). Four contraindications constituted 82.4% of all contraindications. These were delayed ED admission (three hours and beyond in 93 patients-83.0%, and four and a half hours and beyond in 79 patients-70.5%), multilobar infarct, or hypodensity of more than 1/3 of the hemisphere (31 patients-27.7%), uncontrolled hypertension (18 patients-16.1%) and mild or non-isolated neurological symptoms (17 patients-15.2%). Delayed ED admissions constituted 48.2% (44.1% for four and a half hours and beyond) of all contraindications. The details of the contraindications have been presented in Table-II.

Table-II: The distribution of contraindications for thrombolytic therapy of patients.

Contraindications	n	%*
Delayed admission, >2.5 hours	93	84.5
If CT or MRI show a multilobar infarction or a hypodensity>1/3 cerebral hemisphere	31	28.2
Elevated blood pressure (systolic>185 mm Hg and diastolic>110 mm Hg)	18	16.3
Minor and isolated neurological signs	17	15.4
Prior stroke in previous 3 months	7	6.3
History of previous intracranial or subarachnoid hemorrhage	5	4.5
Blood glucose concentration <50 mg/dL or >400 mg/dL	4	3.6
Seizure with postictal residual neurological impairments	4	3.6
Taking an oral anticoagulant or, if anticoagulant being taken, INR >1.7	4	3.6
Major surgery in the previous 14 days	3	2.7
Rapid improving deficit	3	2.7
Myocardial infarction in the previous 3 months	2	1.8
Gastrointestinal or urinary tract hemorrhage in previous 21 days	1	0.9
Evidence of active bleeding or acute trauma (fracture) on examination	1	0.9

*Percent of 110 contraindicated patients. Percents do not total 100 because some patients had more than one contraindication.

DISCUSSION

Successful treatment of acute stroke is directly related to time. The pre-hospital period is the most critical phase and unfortunately, delay occurs commonly in the pre-hospital period. Such issues as being alone or loneliness, inability to notice the first symptoms of stroke by patients or their relatives or nurses, not seeking medical help, transfer to an inappropriate centre and demographical features are effective factors on receiving thrombolytic therapy in this critical period.[6-9] In the literature, the arrival time to the ED of patients using EMS was found to be shorter than the others.[7,10] On the other hand, the arrival time to the ED of those transferred from other healthcare institutions was found to be longer than those that are directly admitted.[11]

In this study, however, no difference was found between ED admissions with ambulance and with private vehicles, and between referrals from other healthcare institutions and admissions to our clinic directly. Using an ambulance and being transferred from other healthcare institutions is not related with early or late ED arrival according to the study by Keskin et al.[12] We think that the problem results from the call time the EMS or the first arrival time to other healthcare institutions. Whereas it was reported in the literature that patients with a high stroke severity have admitted to EDs in a shorter time,[10] no difference was found in our study. There may be a problem of delay in accessing medical care for patients with AIS, arising from the patients and/or their families being unable to recognize the signs and symptoms of AIS. Public and EMS staff education may play an important role in shortening the pre-hospital period, especially when consideration is given to the fact that approximately half of our AIS patients arrive to our hospital from homes that are in rural areas.

Many studies have revealed the fact that acute stroke patients' early arrival to the hospital is always associated with better results.[13,14] However, the most important obstacle in having the thrombolytic therapy seems to be the problem of transfer to an appropriate center in time. Hills et al. stated that only 136 (22%) of 625 acute stroke patients arrived at the emergency room within two and a half hours of the onset of symptoms.[3] Garcia-Monco et al stated that only 16.7% of acute stroke patients presenting to the emergency room in a one year period arrived to hospital within three hours.[15] The only contraindication in 95 (44.4%) of the 214 stroke patients was the problem of not being prepared for

the treatment in three hours according to the study of O'Connor et al.[16]

Qureshi et al confirmed that only 21% of acute ischemic stroke patients were admitted to the hospital in the first three hours.[17] Although rt-PA application over three hours is not suggested in the NINDS study and in the ATLANTIS study, subsequent studies revealed that thrombolytic therapy up to four and a half hours provided favourable outcomes.[18-20] Although the mean arrival time of acute stroke patients varies, the median time is approximately six hours.[7,10] As in our study, 15.2% of the patients arrived to the ED within two and a half hours, with an additional 14.3% arriving within four hours, and an additional 23.2% arriving within six hours. The median value was six hours in accordance with the literature. From this point, it is possible to say that improvements to be made in the critical phase will enable a significant number of patients to receive this treatment. Education of the public and staff in EMS which will be made about acute stroke symptoms through the media or official organizations appear as an important cornerstone in this issue.[21]

In our study, the rate of the patients whose single contraindication for thrombolytic therapy was the inability to be admitted within the approved period of time (< 3 hours), was more than 1/3. The other most frequent contraindications were diffuse infarct area (more than a third of MCA territory or multilobar infarct), uncontrolled HT and mild or rapidly recovering clinical picture, respectively. However, the most frequent contraindication except for delayed ED admission was mild or rapidly recovering clinical picture in the literature.[3,16] Other contraindications have been observed in very small proportions in almost all the studies.[9] Some authors advocate that some of the thrombolytic contraindications are not based on accurate data or that their limits are not clear enough. Therefore, they emphasized the need for revision of these contraindications under the light of new data.[3,22]

CONCLUSION

The primary barrier to the delivery of thrombolytic therapy for AIS is delayed arrival of the patient to a hospital capable of administering thrombolytic therapy to attempt re-perfusion. Given the recent published findings suggesting that rt-PA may be efficacious up to 4.5 hours after the onset of AIS, our data suggest that up to 29.5% of our patients, the percentage arriving within four hours of the onset of stroke symptoms, might be eligible for attempted

re-perfusion. However, to accomplish attempted re-perfusion rates approaching this 29.5% figure, systems must exist to educate the populace and EMS providers to deliver the right patients to the optimal hospital in a clinically useful time frame. Further, to create such an optimal hospital destination for AIS patients will require the availability of intra-hospital efficiencies such as those provided only by a dedicated stroke centre. Currently, there is no legal or physical obstacle for administering thrombolytic therapy to acute ischemic stroke patients in Turkey. The only problem seems to be encouraging the responsible people, and organizing them in a multidisciplinary approach.

REFERENCES

1. Reeves MJ, Arora S, Broderick JP, Frankel M, Heinrich JP, Hickenbottom S, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. Stroke 2005;36(6):1232-1240.
2. Saposnik G, Black SE, Hakim A, Fang J, Tu JV, Kapral MK. Age disparities in stroke quality of care and delivery of health services. Stroke 2009;40(10):3328-3335.
3. Hills NK, Johnston SC. Why are eligible thrombolysis candidates left untreated? Am J Prev Med 2006;31(6 Suppl 2):S210-216.
4. NIH Stroke Scale. http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf Accessed Dec 01, 2010.
5. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke. Circulation 2007;115(20):e478-534.
6. Jones SP, Jenkinson AJ, Leathley MJ, Watkins CL. Stroke knowledge and awareness: an integrative review of the evidence. Age Ageing 2010;39(1):11-22.
7. Kothari R, Jauch E, Broderick J, Brott T, Sauerbeck L, Khoury J, et al. Acute stroke: delays to presentation and emergency department evaluation. Ann Emerg Med 1999;33(1):3-8.
8. Schwamm LH, Reeves MJ, Pan W, Smith EE, Frankel MR, Olson D, et al. Race/ethnicity, quality of care, and outcomes in ischemic stroke. Circulation 2010;121(13):1492-1501.
9. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. Age Ageing 2004;33(2):116-121.
10. Maestroni A, Mandelli C, Manganaro D, Zecca B, Rossi P, Monzani V, et al. Factors influencing delay in presentation for acute stroke in an emergency department in Milan, Italy. Emerg Med J 2008;25(6):340-345.
11. Chang KC, Tseng MC, Tan TY. Prehospital delay after acute stroke in Kaohsiung, Taiwan. Stroke 2004;35(3):700-704.
12. Keskin O, Kalemoglu M, Ulusoy RE. A clinic investigation into prehospital and emergency department delays in acute stroke care. Med Princ Pract 2005;14(6):408-412.
13. Naganuma M, Toyoda K, Nonogi H, Yokota C, Koga M, Yokoyama H, et al. Early hospital arrival improves outcome at discharge in ischemic but not hemorrhagic stroke: a prospective multicenter study. Cerebrovasc Dis 2009;28(1):33-38.
14. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363(9411):768-774.
15. García-Moncó JC, Pinedo A, Escalza I, Ferreira E, Foncea N, Gómez-Beldarrain M, et al. Analysis of the reasons for exclusion from tPA therapy after early arrival in acute stroke patients. Clin Neurol Neurosurg 2007;109(1):50-53.
16. O'Connor RE, McGraw P, Edelsohn L. Thrombolytic therapy for acute ischemic stroke: why the majority of patients remain ineligible for treatment. Ann Emerg Med 1999;33(1):9-14.
17. Qureshi AI, Kirmani JF, Sayed MA, Safdar A, Ahmed S, Ferguson R, et al. Time to hospital arrival, use of thrombolytics, and in-hospital outcomes in ischemic stroke. Neurology 2005;64(12):2115-2120.
18. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant Tissue-Type Plasminogen Activator (Alteplase) for Ischemic Stroke 3 to 5 Hours After Symptom Onset The ATLANTIS Study: A Randomized Controlled Trial. JAMA 1999;282:2019-2026.
19. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359(13):1317-1329.
20. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375(9727):1695-1703.
21. Kim YS, Park SS, Bae HJ, Cho AH, Cho YJ, Han MK, et al. Stroke awareness decreases prehospital delay after acute ischemic stroke in Korea. BMC Neurol 2011;11:2.
22. De Keyser J, Gdovinová Z, Uyttenboogaart M, Vroomen PC, Luijckx GJ. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. Stroke 2007;38(9):2612-2618.

Author's Contribution:

Dr. Sedat Kocak conceived the concept, designed and conducted the study besides drafting the manuscript. Dr. Emine Dogan and Dr. Melek Kokcam were involved in acquisition, analysis and interpretation of the data. Dr. Abdullah S. Girisgin supervised and helped in conducting the study, Dr. Said Bodur was involved in statistical analysis.