ORIGINAL ARTICLE

Tissue plasminogen activator; identifying major barriers related to intravenous injection in ischemic acute cerebral infraction

Fariborz Khorvash[1,2], Fatemeh Heidary[2], Mohammad Saadatnia[1,2], Ahmad Chitsaz[1,2], Zahra Tolou-Ghamari[3]

[1]Department of Neurology, [2]Isfahan Neuroscience Research Centre, Faculty of Medicine, Isfahan University of Medical Sciences, [3]Isfahan Kidney Transplantation Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Background: According to previous publications, in patients with acute ischemic cerebral infarction, thrombolytic therapy using intravenous tissue plasminogen activator (IV-tPA) necessitates precise documentation of symptoms' onset. The aim of this study was to identify major barriers related to the IV-tPA injection in such patients. **Materials and Methods:** Between the year 2014-2015, patients with definitive diagnosis of acute cerebral infarction (n = 180) who attended the neurology ward located at the Isfahan Alzahra Hospital were studied. To investigate barriers related to door to IV-tPA needle time, personal reasons, and criteria for inclusion or exclusion of patients, three questionnaire forms were designed based on the Food and Drug Administration-approved indications or contraindications. **Results:** The mean age of males versus females was 60 versus 77.5 years (ranged 23–93 vs. 29–70 years), respectively. Out of total population, only 10.7% transferred to hospital in <4.5 h after the onset of symptoms. Regarding to eligibility for IV-tPA, 68.9% of total population have had criteria for such treatment. Concerning to both items such as transferring to hospital in <4.5 h after the onset of symptoms and eligibility for IV-tPA, only 6.6% of total population met the criteria for such management. There was ignorance or inattention to symptoms in 75% of population studied. There was a mean of 195.92 ± 6.65 min (182.8–209.04 min) for door to IV-tPA needle time. **Conclusion:** Despite the international guidelines for IV-tPA injection within 3–4.5 h of ischemic stroke symptoms' onset, the results of this study revealed that falling time due to ignorance of symptoms, literacy, and living alone might need further attention. As a result, to decrease death and disability, educational programs related to the symptoms' onset by consultant neurologist in Isfahan/Iran seem to be advantageous.

Key words: Cerebral infarction, injection barriers, ischemic stroke, tissue plasminogen activator

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INTRODUCTION

According to the previous publications, acute ischemic stroke (AIS) could be mentioned as the most reason of events related to death and disability.[1,2] In fact, acute focal cerebral ischemia and sequential dynamism disaster are convoyed by neuronal death in the parts of brain that cerebral blood flow was reduced.[1-4]

Due to rising in the world's prevalence and incidence of stroke, its global importance is increasing extremely.[2,4] Up-to-date epidemiological studies specified that 16.9 million people suffer from stroke each year, which indicates a global incidence of 258/100,000 in each year. However, the number of survivors almost doubled among 1990 and 2010, but there are 5.9 million stroke-associated decreases globally each year.[2,3] Death related to stroke excessively affects blacks, and this inequality is established across all categories of stroke.[5] Age and stroke severity are the main factors of outcomes.[6] Poststroke complications include motor handicaps, dementia, depression, fatigue, and a high risk of early rehospitalization.[3]

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Address for correspondence: Dr. Zahra Tolou-Ghamari, Isfahan Kidney Transplantation Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: toloeghamari@pharm.mui.ac.ir

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The serine protease, tissue plasminogen activator (tPA), as a key enzyme related to fibrinolytic pathway, is involved in disruption of blood clots. Recombinant tPA (rtPA) is a form of tPA that is manufactured by the recombinant biotechnology methods. To achieve reperfusion, intravenous-rtPA (IV-rtPA) is given to the patients to cut the zymogen plasminogen peptide bond into the serine protease plasmin. In addition, tPA plays a role in cell migration and tissue remodeling. Hyper- and hypo-fibrinolysis could be caused by increased or decreased activity which can result in excessive bleeding, thrombosis, or embolism.[6-10] Even though the prescription of tPA for AIS has been increased in the current years, the total degree of its use remains to be low.[11]

Regarding the accurate time for understanding IV-rtPA prescription, the precise records of the last known normal time are vital to confirm an optimum management for stroke patients.[12]

Although publication in 2012 stated that IV-rtPA given within 6 h of stroke onset, another publication in 2013 recommended valuable early administration within 0–3 h, destructive later prescription of 3–4.5 h, and again beneficial of administration of 4.5–6 h.[13-15] Recent approaches mentioned that IV-rtPA therapy could be administered to cautiously nominated patients who can be treated within 4.5 h of AIS onset. Related to the populations that neurologic signs are revealed on awakening (wake-up stroke), they usually are not given IV-rtPA because of the doubt about the time of stroke onset.[16]

Previous studies have shown that IV-rtPA dosed at 0.9 mg/kg with a maximum of 90 mg seems to be safe and effective. Because of the racial variances in blood coagulation-fibrinolysis features, Asian patients might need lower dosage of drug.[16,17] The current international guidelines by the American Stroke Association have established that IV-rtPA should only be given within 4.5 h of stroke onset, and door to needle time should be <60 min, with a goal of 40 min.[18]

Because of time-restriction-injection for IV-rtPA, up to now, there is not any proper guideline associated to the barriers in the IV-rtPA pharmacotherapy approach within the Iranian population of patients with acute ischemic cerebral infarction. Therefore, the aim of this study was to identify the barriers related to the use of IV-rtPA in such population.

MATERIALS AND METHODS

Between 2014 and 2015, patients with definitive diagnosis of acute cerebral infarction who attended the neurology ward located at the Isfahan Alzahra Hospital (n = 180) were studied.

The investigation was approved by the Research Committee of Isfahan University of Medical Sciences (Grant No of 393522). Approach for injection criteria was based on the international guidelines of "Stroke Inclusion/Exclusion Criteria" for injection of IV-rtPA. The barriers related to "door to IV-rtPA needle time" were noted into checklist that was divided into three parts. The first part was included age, sex, date of admission, and literacy for reading and writing. The second part was involved as prehospital information such as onset of symptoms, transfer to hospital (private car/ambulance), arrival time, and the causes of delay to hospital (unavailability of vehicles, ignorance of the symptoms, lack of correct diagnosis, far from hospital, and living alone). The third part was comprised stroke inclusion/exclusion criteria.[19-29] Flowchart 1 shows the barriers for IV-rtPA "door to needle" time taken for each individual patient that was filled by questioner.

All statistical analyses were attempted using the SPSS statistical software package (version 23.0; IBM, Armonk, NY, USA).

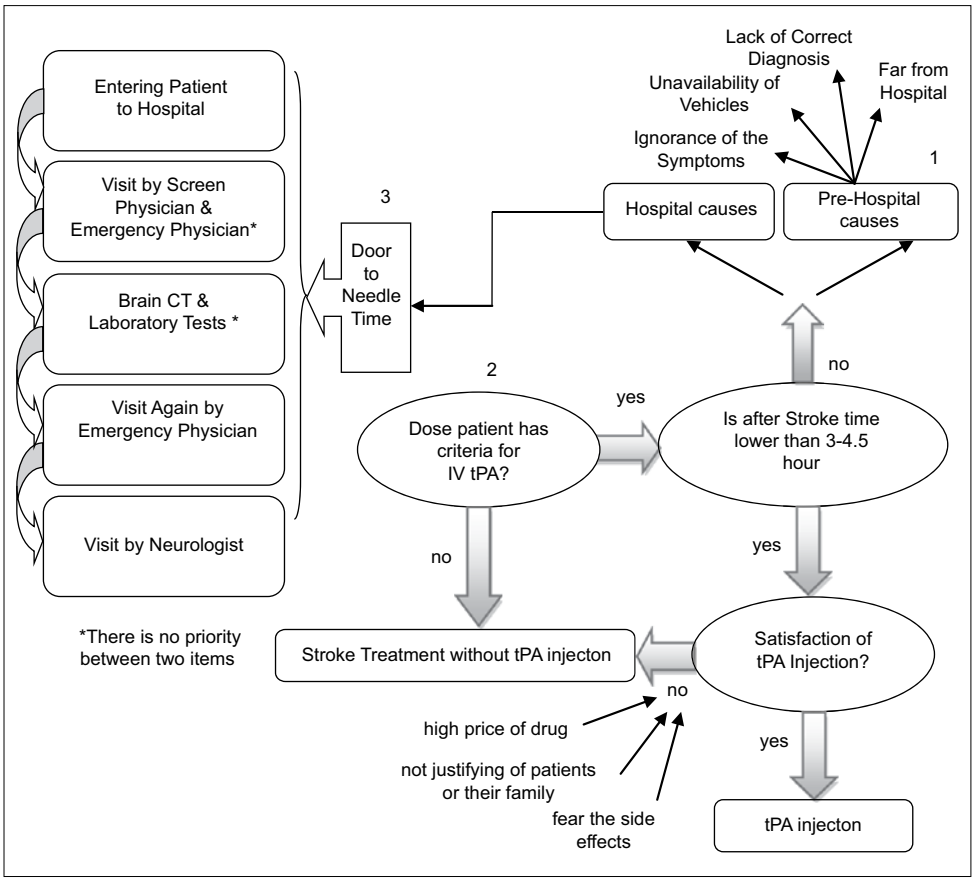
RESULTS

Of the total population referred to hospital, 47.2% were females. As shown in Figure 1, with a mean of 60 years, the minimum and maximum age of females was 29 and 70 years, respectively. Age-related stroke in 75% of females was before the age of 70, in which 31.4% of females ranged from 30 to 60 years.

The mean age of males was 77.5 years (ranged from 23 to 93 years). Age-related stroke in 81% of males ranged from 70 to 90 years [Figure 2]. Table 1 shows the frequency of patients with cerebrovascular accident (CVA), associated to the eligibility for intravenous tPA (IV-tPA) injection. Related to transferring to hospital, 89.3% of patients were not transferred in proper time.

Regarding eligibility for IV-tPA, 68.9% of total population has had criteria for such treatment. Concerning to both items such as transferring to hospital in <4.5 h after the onset of symptoms and eligibility for IV-tPA, only 6.6% of total population met the criteria for such management [Figure 3].

Table 2 shows distribution of inclusion/exclusion criteria items for IV-tPA Injection. There was no evidence related to progressing or worsening of stroke symptoms in 92.2% (n = 166). Related to other neurological deficit, 179 patients did not show any related signs or symptoms. In the beginning of CVA symptoms' onset, 22 out of 180 or 12.2% of



Flowchart 1: Door to tPA needle time

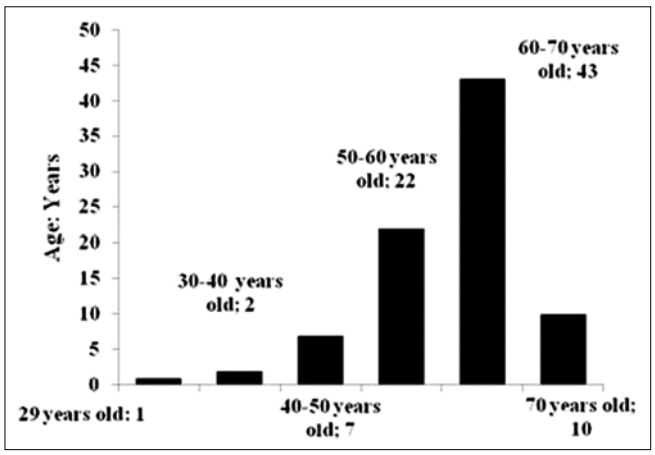


Figure 1: Distribution of age-related stroke in females

patients presented seizures. There was history of intracranial hemorrhage, brain aneurysm, vascular malformation, brain tumor, and brain hemorrhage in 7.8% of patients. There was no sign or symptom related to subarachnoid hemorrhage in 179 patients (99.9%). Only in 4 patients, 2.2% blood glucose was <50 or more than 400 (mg/dl). There was no evidence connected to gastrointestinal hemorrhage or urinary tract problems in 89.9%. Prothrombin time of >15 or internal normalized ratio of prothrombin time of >1.5 was noted in 22 of 180 patients (12.2%). There was not any history of recent anticoagulant therapy in 88.9% of population studied. Only 1.7% ($n = 3$) had platelet of more than 100,000 mm^3. There was no history of trauma or CVA in 92.2%. The previous surgery or blood pressure of ≥185/10 mmHg was reported in 0.6% and 22%, respectively [Figure 4].

Table 3 shows the mean of "door to needle tPA" time taken for population studied. The mean time associated to patients' entry into hospital until to be visited by neurologist was with a mean of 195.92 ±6.65 min (182.8–209.04 min). Time taken for visiting by screen practitioner and emergency was 24.6 ± 2 min (20.7–28.5 min). Procedure related to computed tomography scan, clinical laboratory, and emergency visit was associated to the mean duration of 46.32 ± 2.39 min (41.59–51.06 min). Figure 3 shows distribution of reasons for delay from prehospital to hospital. Out of total population, 105 mentioned that ignored stroke symptoms from the time of onset. There was lack of availability to car for transferring patients to hospital in 62 patients. Literacy or living alone has been noticed in 25 and 34 patients, respectively. There was no pay to attention to disease symptoms in 50 patients. There was difficulty related to long distance from patients' home to hospital in 48 patients. There was a lack of information linked to emergency services and lack of familiarity with the service of 115 in 2 and 18 patients,

Table 1: Distribution of patients eligibility for intravenous tissue plasminogen activator injection

Items answer	Transferred to hospital in <4.5 h	Population eligible for injection	Transferred to hospital in <4.5 h and population eligible for injection
Yes	19 (10.7)	124 (68.9)	12 (6.6)
No	161 (89.3)	56 (31.1)	168 (93.4)

Table 2: Frequently distribution of inclusion/exclusion criteria items for IV-tPA injection

Q1: Is there any evident related to progressive symptoms In 14 patients were positive (7.8%)
Q2: Is head CT is positive for hemorrhage? In 6 patients were positive (3.3%)
Q3: Is there any evident related to seizure at onset In 22 patients were positive (12.2%)
Q4: Is there any evident related to neurological disorder? In 1 patients were positive (0.6%)
Q5: Is there any evident related to symptoms findings suggesting ICH, SAH? In 1 patients were positive (0.6%)
Q6: Is there any history of intracranial hemorrhage or brain aneurysm or vascular malformation or brain tumor In 14 patients were positive (7.8%)
Q7: Is there any evident related to recent active internal bleeding (less than 22 days)? In 2 patients were positive (1.1%)
Q8: Is there any history of blood glucose <50 or >400 mg/dl? In 4 patients were positive (2.2%)
Q9: Is there any history of anticoagulant therapy before admission? In 20 patients were positive (11.1%)
Q10: Is there any history of PTT >40; INR >1.7? In 22 patients were positive (12.2%)
Q11: Is there any evident related to platelets <100,000? In 3 patients were positive (1.7%)
Q12: Is there any history of heparin use within 48 hours? In 22 patients were positive (12.2%)
Q14: Is there any history of major surgery or trauma within 3 months In 1 patient were positive (0.6%)
Q13: Is there any history of recent intracranial or spinal surgery, head trauma, or stroke (less than 3 months) In 14 patients were positive (7.8%)
Q15: SBP >185 or DBP >110 mm Hg? In 4 patients were positive (2.2%)

respectively. There were reasons of delay due to ignorance or inattention to stroke symptoms because of literacy in 75% of patients population studied.

DISCUSSION

The result of this study confirmed a minimum age of around 25 years of life for the event of stroke (classified as acute ischemic cerebral infarction) in both genders. This is in agreement with previous publications, in which noted that changes in (1) endothelial function, (2) alterations in the blood–brain barrier, or (3) hormonal changes could be considered for such patients with young age-related stroke.[28-31]

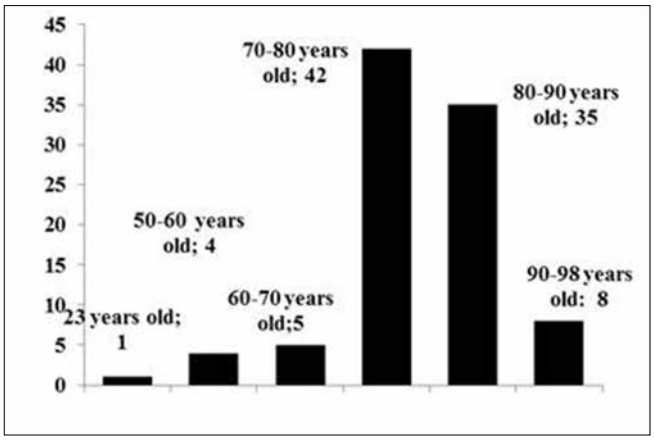


Figure 2: Distribution of age-related stroke in males

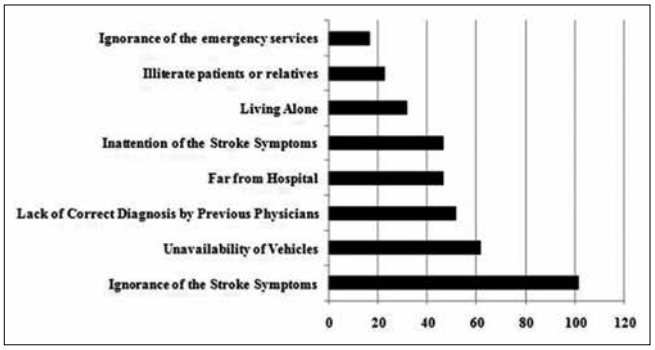


Figure 3: Distribution of reasons for delay from prehospital to hospital

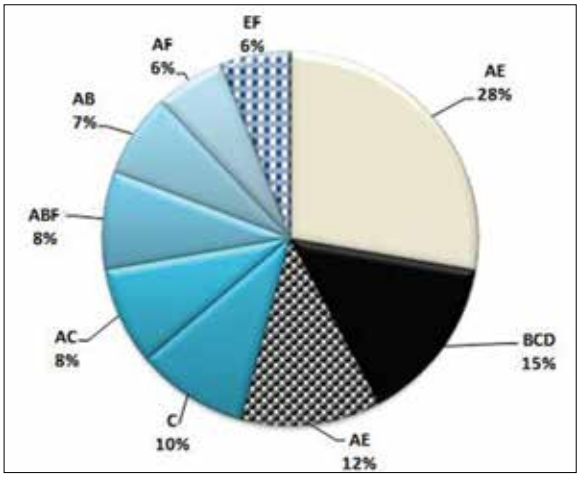


Figure 4: Co-incidents of reasons of delay from prehospital to hospital

Linked to clinical care for patients with acute ischemic cerebral infarction, pharmacotherapy management, and device-induced reperfusion has established as optimistic management related to the both reperfusion effectiveness and 3 months functional results after AIS. Actually, IV-tPA was first approved in the United States in 1996 and shown to have a positive impact related to clinical outcome in recent years. In 2012, the stroke academic industry roundtable suggested beneficial assessment of (1) neuroprotective agents, (2) IV-tPA,

Table 3: Mean of "door to IV-tPA injection time taken" for population studied (*n*=180)

Time (min)	Enter to hospital	Screen physician visit	Emergency visit	Brain CT and clinical libratory	Emergency visit again	Neurology visit
Mean±Std. error Mean		24.62±2.00 (20.66-28.58)		16.41±4.04 (24.4-8.43)		
		31.02±1.48 (28.10-33.95)				
			55.11±3.22 (48.75-61.47)			
			71.52±2.95 (65.7-77.35)			
				46.32±2.39 (41.59-51.06)		
				27.24±4.02 (19.31-35.17)		
					66.11±5.51 (55.22-77)	
				111.83±6.21 (99.56-124.1)		
					93.36±6.98 (79.56-107.15)	
				195.92±6.65 (182.79-209.04)		

and (3) emerging treatments to decrease reperfusion damage.[1-31] Henninger and Fisher reported that <10% of all patients with AIS receive intravenous thrombolysis and it has been expected that only around 7%–15% of AIS patients are qualified for acute endovascular intervention.[29]

Investigation of barriers related to the use of IV-tPA in the treatment of patients with CVA, from prehospital to hospital, showed inattention of patients to their symptoms at the time of symptoms' onset, in which the reason in 30% was due to living lonely. There was lack of correct diagnosis noted in 33% of patients. Unavailability for a car to transform patients to a proper hospital was noted in 30%. Publication in 2015 confirmed that IV-tPA therapy could be prescribed to carefully selected patients and those could be administered within 4.5 h of AIS onset. Associated to populations that neurologic signs are exposed upon wake-up stroke typically, because of the uncertainty about the time of stroke onset, IV-rtPA should not be prescribed.[16]

There was a mean falling time of 3.3 h within hospital (95% confidence interval of 3.0–3.5 h). A previous publication by Spokoyny *et al*., in 2015, highlighted the necessity for informative package associated to the determination and modification of the certain time of stroke onset, particularly at hospital without stroke expertise.[10]

Finally, however, this study revealed barriers for door to IV-tPA injection, but its limitation could be mentioned as the lack of stroke data registry to generate standard model that could be adjustable to Isfahan/Iran health-care system.

CONCLUSION

Due to the ignorance of symptoms in 75% of patients, educative programs in television or other communicative media, by neurologist in terms of explaining stroke symptoms and its disaster disability consequences, should be more considered. It is also important for healthcare staff to understand the importance of protocol guidelines toward IV-tPA prescription in proper time.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

- FKH contributed to the conception of the work, conducting the study and revising the draft, approval of the final version of the manuscript and agreed for all aspects of the work.
- FH contributed to the conception of the work, conducting the study and revising the draft, approval of the final version of the manuscript and agreed for all aspects of the work.
- MS contributed to the conception of the work, conducting the study and revising the draft, approval of the final version of the manuscript and agreed for all aspects of the work.
- AC contributed to the conception of the work, conducting the study and revising the draft, approval of the final version of the manuscript and agreed for all aspects of the work.
- ZT contributed to the conception of the work, conducting the study and revising the draft, approval of the final version of the manuscript and agreed for all aspects of the work.

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