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Research Article

DETERMINATION OF THE ELIGIBLE PEOPLE PERCENT TO RECEIVE INTRAVENOUS TPA IN PATIENTS WITH ACUTE STROKE

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ABSTRACT
Stroke is the most common cause of disability and the third leading cause of death after heart disease and cancer in the world, which is a significant cause for the disease. According to the World Health Organization estimates in 2008, 5.5 million people died as a result of stroke, in which 20% occurred in South Asia. Based on the current study, among the inhibitor factor to receive plasminogen activator, delay in calling a neurologist with 75% has the highest frequency, while 4% of patients who was visited by a neurologist were eligible to receive the drug. In this case, the eligibility for injection of 8% reach to 12%, that is equivalent to a 50% increase in the eligibility.

Keywords: *World Health Organization, Eligible People Percent, Acute Stroke*

INTRODUCTION
Stroke is the most common cause of disability and the third leading cause of death after heart disease and cancer in the world, which is a significant cause for the disease (Antony, 2009). According to the World Health Organization estimates in 2008, 5.5 million people died as a result of stroke, in which 20% occurred in South Asia (Katzan *et al.*, 2000). Prior to this, occurrence of stroke in young people, were 3%, which of course, this group of people were included under 45 years, but now we can say this amount reached to 7 to 8 percent in this age group, always brain vascular disease play very important and widespread role in mortality and disability (morbidity of adults at risk, and also it has social and economic burden and rehabilitation problems, although stroke is related to the brain disease but affects the whole body (Khealani *et al.*, 2008). Clinically stroke involved variety of defects, including changes in the level of consciousness, mental disorders, motor, cognitive, perceptual, language function, pain and psychological problems such as depression (with a prevalence of 14.1% to 19.3%), it reduce the recovery and rehabilitation, and even may lead a person to commit suicide.

Stroke defined as a syndrome characterized by acute onset of neurological disorders for at least 24 hours, it is reflection of local involvement of the central nervous system, and results of impaired circulation to the brain. There are usually no warning signs before a stroke or symptoms of a stroke should be greatly minor. Usually, after stroke, patient must be admitted immediately to avoid permanent damage to the brain. Complications after a stroke depends on stroke location and extent of brain affected tissue. The stroke effects involved mild and transient side effects such as blurred vision to permanent crippling complications or even deaths (Michael and Aminoff, 2011). The tissue plasminogen activator (tPA) is a serine protease with the corresponding gene on chromosome 8 (12p 8) in human, it catalyze conversion of plasminogen to plasmin, this property contains its ability to break down fibrin clots as clots available in cerebral vascular thrombotic lesions (Spetzler and Nehls, 1987) preparation of tPA synthesized using recombinant DNA techniques and circulating half-life of tPA is four minutes. The FDA in 1996 permitted it's intravenously injection at the first three hours of a stroke. After discarding the latest European study of people over 80 years and a severe stroke and diabetes have achieved good results by injection of 3 to 5.4 hours after the onset of stroke (Thomas *et al.*, 1988).

The Clinical Use of Tissue Plasminogen Activator (tPA)
In America and in Europe a period of three and, 5.4 hours after the onset of the disease, have allowed injection of tPA. Most centers for mild stroke which have a good prognosis, tPA is not injected and in cases with serious symptoms such as aphasia and hemianopia and in cases where there is frequent mild symptoms, tPA is injected (Rezazadeh *et al.*, 2013). In cases where the systolic blood pressure and

diastolic is over 185 and 110 mmHg, the drug should not be administered before controlling blood pressure. All patients must undergo CT scans of stroke. In cases of cerebral hemorrhage and infarction of more than 30% in a hemisphere, it should not be injected. In Extensive infarction there is high risk of bleeding and low risk of complications return.

In all cases in blood tests the numbers of platelets have to be over a hundred thousand, PT over 15 and blood glucose of more than 50 mg per 100 ml of blood (Bambauer *et al.,* 2006). Patient family should be aware of the limited useful effects of treatment (maximum 11 to 13 improvement points occur in the symptoms of a stroke) and the probability of a serious risk of escalation, including stroke and brain hemorrhage leading to death in 6% of cases should be noted.

The recommended treatment dose of 9.0 mg per kilogram of body weight is the maximum amount of 90 mg. 10% of drug injected in the first minute and the rest within 60 minutes. Lower doses of the drug (6.0 mg for each Kg weight) in Japan have good results.

For injection, the patient should be admitted in brain I.C.U, while the injection until 24 hours after the injection, the patient's blood pressure and nerves vital signs must be controlled, in the early hours of 15 to 30 minutes after every hour of patient examination was performed, in case of exacerbation of neurological symptoms, treatment must be stopped, and the brain CT scan is necessary to ensure brain hemorrhage, in the absence of hemorrhage after 24 hours other therapies to prevent stroke, is prescribed. In cases where the response to treatment is not optimal and needs to be injected intra-arterial or remove clots required by catheter CT angiography is performed (Katzan *et al.,* 2004; Grotta *et al.,* 2001). The requirements of the administration of tissue plasminogen activator in the patients with cerebral ischemic stroke as outlined in the following table:

Table 1: Requirements to Receive a Tissue Plasminogen Activator

Stroke length <3 hours in some resource of <5.4 hours	Absence of head trauma, stroke or heart attack in the last 3 months
The lack of digestive or urinary hemorrhage in the last 21 days	No active bleeding and no evidence of acute trauma
Having no major surgery in the last 14 days	No history of intra cerebral hemorrhage
Lack of oral anticoagulant	Lack of seizures at the start of stroke
No signs of subarachnoid hemorrhage	There is no evidence of postictalsymptoms
Systolic blood pressure <185	Diastolic blood pressure <110
INR <1/7	Lack of heparin in the last 48 Hours
PTT< 50	Platelet count> 100,000
Serum Glucose <400 and <50	No evidence of intracranial hemorrhage
Lack of NIHSS <4 or NIHSS> 25	Lack of widespread conflict (3/1 cerebral hemispheres)

In this project, we therefore aimed at to determine the percentage of people eligible to receive intravenous tPA to examine the factors that contributed to delaying referral and evaluation of patients, and thus, drop it from the list of possible recipients of the drug.

It is obvious that identifying and correcting these factors can pave the way for applying this medication in Qazvin hospitals emergency (Kentaro *et al.,* 2009).

Review of the Literature

In an article titled, using a variety of tissue plasminogen activator for acute ischemic stroke, that was conducted by Katzan (1998) noted that in December 1995 the International Committee of neurological and stroke disease (NINDS), the study group on the rtPA and stroke, reported IVtPA usefulness in

patients with acute ischemic stroke, that referred period less than 3 hours. The FDA in 1996 approved the use of intravenous tPA. The use of this drug applied a dramatic change in the way of dealing with patients with acute ischemic stroke, but these drugs increase the risk of intracerebral hemorrhage.

This study has investigated the use of intravenous tPA, the incidence of symptomatic intracranial hemorrhage and outcomes in admitted patients, so that about 3948 patients diagnosed with primary brain ischemic stroke were admitted and amount of intravenous tPA and intracranial bleeding in patients who were treated with this drug and hospital mortality in patients who have received the drug compared with the mortality predicted by existing models have been studied.

According to the results of 70 patients (8/1%) of patients with acute cerebral ischemic stroke received intravenous tPA, among these11 patients approximately 7/15% of patients affected by symptomatic intra cerebral hemorrhage and 50% of patients were inconsistent with international solutions, and hospital mortality between patients who were treated with tPA were (7/15%) compared with patients who did not receive the drug (1/5%) as compared with forecasts conducted on models (9/7%) markedly were higher, in fact, a small proportion of patients with acute cerebral stroke received the drug experienced a high rate of intracranial hemorrhage, such findings may be different from clinical trials (Peter, 2008; Michael and Aminoff, 2007).

A research conducted by Heuschmann *et al.,* (2002 and 2004) with the objective of estimating mortality predictors in patients with acute cerebral stroke who received intravenous tPA, carried out in the form of observational cohort on 1,658 patients with acute cerebral stroke. The finding show that 10% of patients who received the drug has died in hospital that 5/67% of mortality occurred in the first 7 days so predictive factors of hospital mortality in patients after receiving tPA include getting old and the high level of loss of consciousness (Gregory, 1988).

The overall rate of symptomatic ICH were 1/7% that increased with getting old, a negative correlation between the number of people who have been treated in the hospital with tPA and the risk of hospital death was observed (Michael and Aminoff, 2011).

In a study conducted by Bambaure and colleagues (2006), they examined the cause of receiving tPA in a few patients who attended with acute ischemic stroke. The study found that stroke is the third most common cause of death in the United States of America and tPA improve more than 50% of stroke symptoms and lower rate of complications, therefore, only 3 to 8/5% of those potential candidate of tPA are receiving the medicine.

Ideally should more than 40% of all patients with stroke receive tPA. This study by reviewing of other reports, has suggested three major barriers to greater use of tPA: poor awareness of stroke symptoms, physicians fear of legal issues and inadequate funding for facilities and personnel requirements. Demography of United States of America has shown that knowledge about stroke is very small. They do not recognize stroke symptoms and in case of such symptoms do not receiving emergency care (Roether, 2004).

Samer Aldandashi and colleagues (2007) carried out a study in three parts, the part A, showed the effect of anti platelet to evaluate the volume of infarct, B reviews impaired perfusion and Part C showed the effect of anti platelet treatment and combination with tPA. Part C showed that dipyrimole with tPA and tPA plus aspirin, compared with tPA alone will significantly reduce infarct size (Spetzler and Nehls, 1987).

Kentaro and his colleagues (2011) conducted a study. In this study, changes in the expression of repair factors and neurodegenerative in the effect of tPA and eliminate free radicals after cerebral transient ischemia, were assessed. Methods show that physiological saline or edaravone 2 times injected during the 90 minutes after occlusion of MCA in rats.

Then, using similar saline or tPA in reflowing size of the infarct and protein factors associated with the restoration and neurodegenerative were investigated.

The results of the study show that tPA reduced protein factor involved in the inhibition and further out growth of axon (Katzan *et al.,* 2004).

A study by Hussein-Zadeh and colleagues (2012) investigated the effects of mechanical controls of brain blood flow on embolic stroke model administered after the delayed-therapy with tissue plasminogen activator on ovariectomized rats.

The study carried out on 32 female rats in 4 control group in a way that at first ovariectomized animals a month after stroke was induced by a clot in to the middle cerebral artery, tPA carried out in 6 hours MFC (Mechanical Flow Control) in 5 stages, 30 seconds and 30 seconds to closing and opening of the common carotid arteries in six and a half hours after stroke induction.

Infarction volume, cerebral blood flow and neurological disorders were measured and compared two days after induction of stroke.

The results included an increase in infarct volume compared to controls in tPA and in tPA + MFC group significantly reduced. Although delayed injection of tPA, increased blood flow to the brain and neurological disorders, but using MFC in the 30 minutes after the injection of tPA, reduced cerebral blood flow and neurological disorders so MFC following delayed administration of tPA has neuroprotective effect (Antony, 2009).

Hypotheses or Research Questions

1. In case of on time referring to the emergency room does most of patients with acute cerebral stroke will be eligible to receive intravenous t-PA?
2. Do prolonging the initial assessment and providing diagnostic commands by health workers are inhibitive causes to on time delivery oft-PA?
3. Does prolongation of time to prepare required clinical results are inhibitive causes for on time injection of t-PA?

MATERIALS AND METHODS

Methodology and Research Design

This study was conducted in 2014 in Qazvin Boali cina hospital emergency and information needed for the project was included in a questionnaire and gathered for each patient in the emergency room by the Executive of the project.

In the questionnaire (Appendix A) all Clinical and laboratory factors needed to consider the necessary conditions for the administration of t-PA which is entered in the form of patient records by determining their registration time. In this study, all patients who are admitted with ischemic stroke were examined and people with cerebral hemorrhagic stroke were excluded. So that about 100 patients with cerebral ischemic stroke for eligibility to receive intravenous tPA treatment based on the items listed in the questionnaire were evaluated. All information obtained from the questionnaires was used for statistical analysis.

RESULTS AND DISCUSSION

Results

Based on the results of the study, the mean age of patients with cerebral ischemic stroke was about 64 years. The risk factors in these patients were as follows:

Table 2: The Frequency of Risk Factors for Stroke

Risk Factor	The Frequency of Risk Factors
Blood Pressure	77%
Diabetes	53%
Ischemic Heart Disease	56%

Early symptoms of stroke in these patients show that 80% of hemiparesis, 11% of imbalances, 5% with aphasia and 4% with vertigo had been admitted, of which 29% were improving, 37% worsening and 34% unchanged symptoms.

Table 3: Percentage Frequency of Risk Factors for Bleeding

Factors Risk	Percentage Frequency
Gastrointestinal or Urine Bleeding in 21 days	6%
Major Surgery within the last 14 days	0%
A History of Head Trauma, Cerebral or Heart Stroke in the last 3 months	6%
History of Cerebral Bleeding	5%
Signs of Cerebral Bleeding	0%
Active Bleeding or Signs of Acute Trauma	0%
Subarachnoid Hemorrhage Symptoms	0%
Taking Anticoagulant	26%
Antiplatelet Drugs	35%
INR more than 7.1	3%
PTT more than 50	6%
Platelet Count below 100000 ml	7%
Systolic Blood Pressure more than 185mmHg	6%
Diastolic Blood Pressure greater than 110mmHg	6%

As outlined in Table 3, the frequency of risk factors that put patients at risk of bleeding and prevent from receiving the drug is listed.

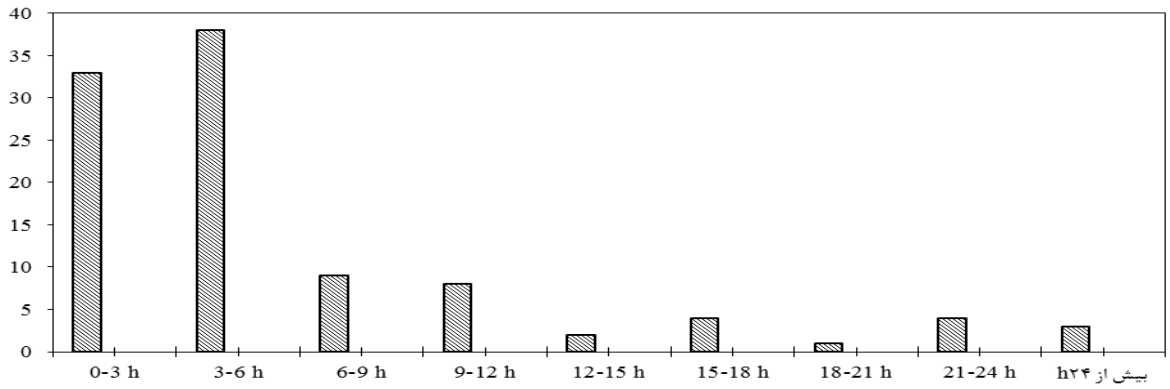

Figure 1: The Patient's Referring after Stroke Symptoms

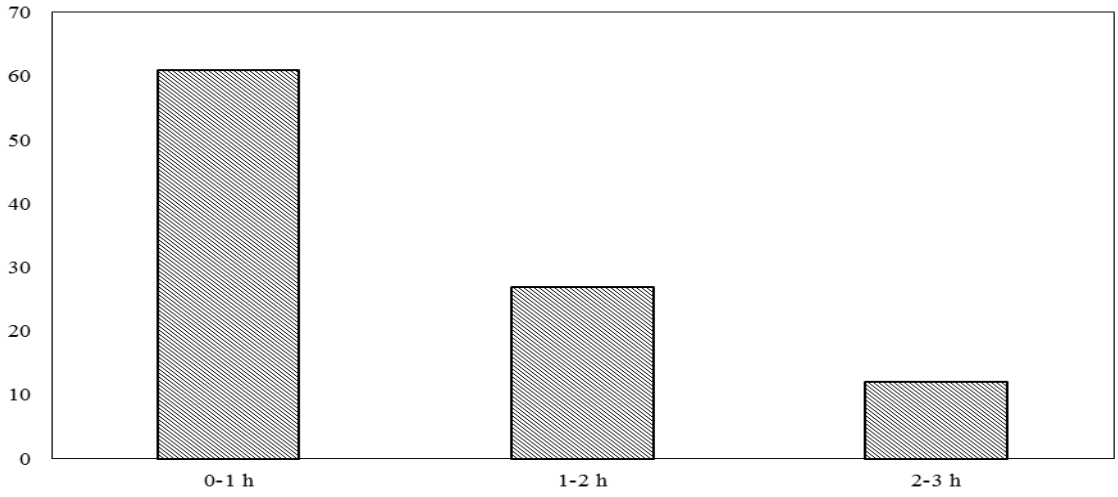

Figure 2: The Percentage Frequency of Patient Visit by Emergency Physician

Table 4: The First Visit by a Neurologist after Patient Referring

Time	The Percentage Frequency of Patients Visited by Neurologists
0 to 3 hours after referring	25%
3 to 6 hours after referring	18%
6 to 9 hours after referring	20%
9 to 12 hours after referring	18%
12 to 15 hours after referring	5%
15 to 18 hours after referring	6%
18to21 hours after referring	5%
21to24 hours after referring	0%
More than 24 hours	3%

Table 5: The Percentage Frequency of Preparing Tests after Patients Referring

Time	The Percentage Frequency of Patients Visited by Neurologists
0 to 3 hours after referring	25%
3 to 6 hours after referring	18%
6 to 9 hours after referring	20%
9 to 12 hours after referring	18%
12 to 15 hours after referring	5%
15 to 18 hours after referring	6%
18to21 hours after referring	5%
21to24 hours after referring	0%
More than 24 hours	3%

Table 6: The Percentage Frequency of Preparing Patients CT Scan after Referring

Time	The Percentage Frequency of Prepared Tests
0 to 3 hours after referring	64%
3 to 6 hours after referring	18%
6 to 9 hours after referring	7%
9 to 12 hours after referring	6%
12 to 15 hours after referring	1%
15 to 18 hours after referring	2%
18to21 hours after referring	0%
21to24 hours after referring	0%
More than 24 hours	1%

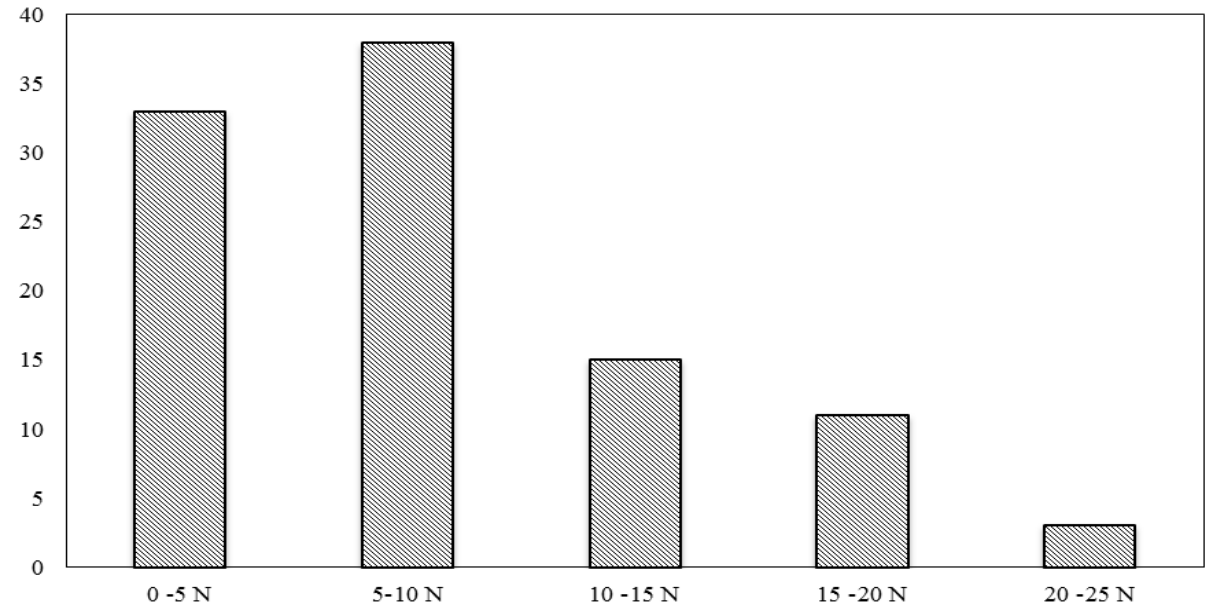

Figure 3: The Percentage Frequency of Patients with NIHSS

As can be seen, most patients (71%) had NIHSS between 0-10.
If only 4% of patients were seen by a neurologist in 3 hours were eligible to receive the drug. None of the patients had evidence of seizure or postictal symptoms during stroke and their glucose was not less than150d/ mg or more than 1400 d/mg.
About 15% of patients had NIHSS <4 or NIHSS> 25, and in 20% of patients the ischemic involvement in the cerebral hemispheres were 3/1.
Finally, 8% of patients were eligible to receive intravenous tPA. In the following graph percentage frequency of causes due to the lack of receiving tPA were briefly presented.

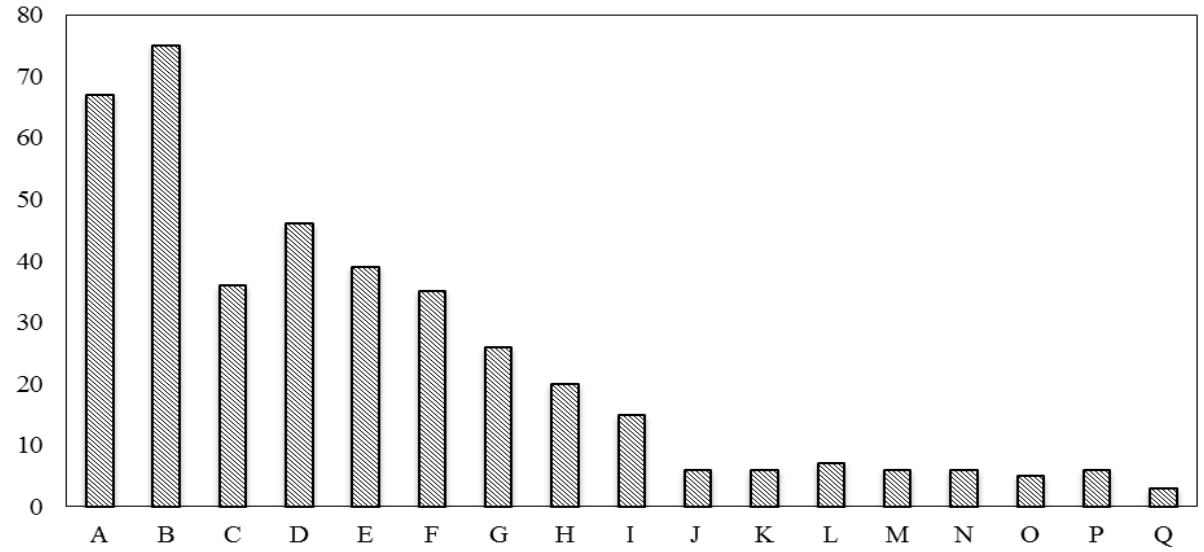

Figure 4: The Percentage Frequency of Inhibitors from Receiving tPA

In this chart, we have:

Symbol	Definition	Symbol	Definition
A	A delay in referring	J	History of head trauma, stroke or heart attack in the last 3 months
B	Delays in neurologist visit	K	50PTT>
C	Delay in preparing CT scan	L	Platelets <100,000
D	Delay in preparing experiments	M	Systolic blood pressure> 185
E	Delay in patients visit by emergency physician	N	Diastolic blood pressure> 110
F	Taking antiplatelet drugs	O	History of cerebral bleeding
G	Taking anticoagulant drugs		Urinary or gastrointestinal bleeding in the last 21 days
H	Extensive involvement in brain hemisphere (1/3	P	INR >1/7
I	NIHSS> or 25 NIHSS<4	Q	

Discussion

As mentioned above, according to the study, the mean age of patients with acute ischemic stroke was 64 years that is nearly close to the an average age of 68 years in Grotta and colleagues study in 1996-2000-1996 which was equal to 68 year (Bambauer *et al.*, 2006). While the number in L. Saver and *et al.*, (2013) study was equal to 72 years (Khealani *et al.*, 2008). This number in study of Hatamabadi and colleagues was 7/59 years (Thomas, 1988). The most common symptom of patients referring with cerebral ischemic stroke was hemiparesis (80%), worsening symptoms (37%) and no change (34%), which seems to have been the cause of more patients in 6 hours after the onset of symptoms (33% in 3 first hours and 38% at 3 second hour of Figure 1 refer to emergency room. The results of the study in 1999-2000 by Katzan and colleagues noted that 15% of patients with ischemic stroke were referred within 3 hours. Its inhibitors common cause were mild neurologic deficit and rapid improvement of symptoms (Spetzler and Nehls, 1987). In fact, in general, the more pronounced and the more dangerous disease symptoms, the more rapid patient referring to the hospital and health centers. According to Figure 1 that about 3/1 (33%) patients referred in the period of 3 hours, but most patients have ranged over 3 hours (67%), so delay in patients referring, continues to be an important factor in lack of receiving the drug is, of course, the delay occur due to the lack of awareness of the importance of cultural problems mentioned in the studies or the long way to go to health centers. Of course due to the center of Bu-Ali is the only stroke center in Qazvin and due to weather conditions and long distance, the functions of this factor are significant in delay. 61% of patients at 1 hour after referring was visited by the emergency physician (Figure 1) and 39% over 1 hour, so it can be said that delay in the appointment of patients with acute ischemic stroke in view of emergency physician are among the main causes of the inhibitors of the drug. In this study, 4/1 (25%) (Table 4), patients in the first 3 hours after referring, having been examined by a neurologist physician, in fact 75% have been visited in the period of more than 3 hours in fact, as It seems that neurologist visit is the most important factor in lack of getting the drug by patients, but the center is not equipped with tissue plasminogen activator, so patients who are eligible to receive the drug, exit from emergency conditions and visited as semi-emergency after initial actions by a neurologist. In addition, 4% of patients if were seen by a neurologist in a period of 3 hours, were eligible to receive the drug, so the delay in referring of the patients with acute ischemic stroke continue to be the most important prohibitive factor in getting drugs. Examination of referring patients for evaluation of blood sugar, PTT and INR in 54% of patients (Table 5) having been prepared in the first 3 hours after referring, in 46% of patients, examination has been prepared over 3 hours after referring and indicate that the delay in preparing experiments to neurologist visit delay and delay in referring to the hospital by the patient has less important in preventing tissue plasminogen activator, but it is still has a special status in non-receiving of drug by patients with acute stroke, because almost half of the initial examination was prepared in the period of over 3 hours.

Initial CT scans of patients with ischemic lesion to determine the presence or absence of cerebral bleeding and old brain damage in 64% (Table 6) of patients have been prepared in the period of 3 hours after referring. In fact, in 36% of patients CT scan has been prepared with delay, so delay in preparing the CT scan compared to delay in referring of patients visiting of neurologists and preparing experiments placed in the lower ranks and relatively has less important in the prevention of receiving tissue plasminogen activator in patients with cerebral ischemic stroke. However, this does not mean that it is negligible and is still classified as one of the most important factors in getting a drug. In the study of Hatam Abadi *et al.*, the average time between arrival of patient to the emergency room to the visit, CT scans, neurological consultation and the final decision for the patient was, respectively 11, 112, 211 and 320 minutes (Roether, 2004). It should be noted that factors such as visit delay by a neurologist and emergency physician, delays in preparing examinations and CT scans, if prescription of the drug carried out at the center of Bu Ali intervention could be occurred easily. NIHSS criteria for patients with cerebral ischemic stroke individually calculated that 33% of patients had NIHSS 0 to 5 and 38 %of patients had NIHSS between 5 and 10. In fact, we can say that most patients (71%) had NIHSS were between 0-10, while the study of L. Saver that was conducted in 2013, the criteria for recorded NIHSS before treatment in /87/7% patients, was 11%, respectively. In the study by James C. Grotta and colleagues (1996-2000), 15% of all patients with acute cerebral ischemia were examined before treatment by NIHSS criteria which was 6 ± 14 and amount of NIHSS in people who was affected by hospital mortality (15%) was equal to 7 ± 7 (Gregory, 1988). Finally, about 8% of the patients were eligible for receiving tissue plasminogen activator, this amount was nearly close to Katzan study (1999-2000), according to the study 9/6% get qualified to receive the drug. However, these rates are less than the amount obtained in the study was conducted by Grotta and colleagues (1996-2000). On the basis of this study tPA therapy can be prescribed for more than 15% of patients with in acute cerebral stroke, that is usually associated with low risk of symptomatic brain hemorrhage which is dependent on examining and organizing treatment teams and adherence to published guidelines (James *et al.*, 2012). In a study conducted by Bambaure (2006) indicated that ideally more than 40% of all patients with stroke should receive tPA (Rezazadeh *et al.*, 2013). In a study by Hatamabadi and colleagues, the causes were lack of drug injection in 104 cases (70/3%), losing the golden time, in 31 patients (20/9%) drug inhibition in 8 patients (4/5%) lack of intensive care beds and in 5 patients (4/3%) lack of financial afford. Based on the current study, among the causes of inhibitors for receiving plasminogen activator, the delay in calling a neurologist with 75% (Figure 4), has the highest frequency, while 4% of patients in case of neurologist visit were eligible to receive drug. In this case, the eligibility for the injection of 8% reach to 12%, that is equivalent to a 50% increase in the eligibility. Although this amount is significant, but it could easily change and interfere. This delay may be due to lack the injection of tissue plasminogen activator in this center and the neurologist could visit the patient in non-emergency room. Therefore, given that the delay is not going to intervene and change, amount of 67% continues to be the most important preventive factor in drug receiving.

Delays in preparing experiments with 46% and delay in the visit of emergency physician with (39%) and delays in preparing CT scan with 36% placed in the following ranking respectively. As mentioned earlier, all these factors other than delay in referring easily intervene and if this center administer injection of tissue plasminogen activator, the only thing that seems does not interfere and causes the most difficult feature in the administration of the drug to patients, is delays in referring. Anti platelet and anticoagulant drugs respectively with 35% and 26% are the important factor in the next rank.

Among this, the broad involvement of the cerebral hemispheres (1/3) with 20% NIHSS> 25 or NIHSS <4 with a frequency of 15%, also are important. In the study conducted by Hatamabadi *et al.*, the causes of injection in 31 patients (9/20%) were drug interaction. It should be noted that the causes of lack of receiving of tissue activator, is a multi-factorial and dependent on several. Thus, most patients had several inhibitors reasons at the same time. Among the factors that predispose to bleeding, such as platelet count> 100,000 with 7%, followed by systolic blood pressure> 185, diastolic blood pressure> 110, a history of head trauma and stroke and heart attack, history of urinary or gastrointestinal bleeding in the last 21 days,

PTT> 50 each with a frequency of 6%, and a history of cerebral hemorrhage with 5% and 1.7 INR>with (3%) were less important.

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