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Research Article

Intravenous Thrombolysis in Acute Ischemic Stroke: Experiences in Dokuz Eylül University Hospital, Medical Faculty, Department of Neurology

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Abstract

Acute stroke is the second leading cause of death after heart diseases in the world. Acute ischemic stroke (AIS) accounts for 80% of all strokes. The idea that AIS is an incurable disease has been abolished during the recent years because of thrombolytic treatment. To date, the only proven therapy in acute ischemic stroke to prevent infarction and minimize the degree of permanent brain injury is thrombolytic treatment. But it has some limitations; it has narrow theuropatic index and high risk of serious complications and also well-established stroke centers are needed for this therapy. We present 21 patients with acute ischemic stroke (13 male, 8 female) who were treated with intravenous recombinant tissue plasminogen activator (IV rt-PA) in our department between 19.09.2006 – 30.01.2008. The neurological statuses of the patients were assessed by "The National Institutes of Health Stroke Scale" (NIHSS) before thrombolysis application, at 24 hour, at 1 week and at 3 months. At the first day of the therapy, 75% of patients had excellent global outcomes (minimal or no deficit). The neurological examinations of IV rt-PA patients at 1 month and at 3 months were also excellent. Symptomatic intracranial bleeding was occured in one patient as a result of IV rt-PA threapy. Four patients were died, one patient died because of brain edema without hemorrhage, one patient died because of brain hemorrhage, the others died because of systemic reasons. Despite low number of patients, our experience contributed important information that IV rt-PA treatment is effective and reliable in well-selected patients.

Keywords: Acute ischemic stroke, thrombolytic treatment

Akut İskemik İnmede Trombolitik Tedavi:Dokuz Eylül Üniversitesi Tıp Fakültesi Hastanesi Nöroloji Anabilim Dalı Deneyimi

Özet

Akut inme (Aİ), dünyada ölüme ve sakatlığa yol açan hastalıklar içinde en başta gelenlerindendir. Kalp hastalıklarından sonra dünyada ölüme neden olan hastalıklar arasında ikinci sırada yer almaktadır. Tüm inmelerin %80'ini iskemik inmeler oluşturur. Son yıllarda akut iskemik inme tedavisinde trombolitik tedavinin uygulanmaya başlamasıyla inmenin tedavi edilemez bir durum olduğu görüşü yıkılmıştır. Bugün için, iskemik inmede beyin kan akımını tekrar sağlamak, iskemik hasarı azaltmak ve nörolojik dizabiliteyi sınırlamak için yapılabilecek en önemli tedavi girişimi akut dönemde uygulanan sistemik trombolitik tedavidir. Tedavi penceresinin oldukça dar olması, ciddi komplikasyonların ortaya çıkabilmesi ve donanımlı merkezlere gereksinim duyulması bu tedavi şansına sahip hasta sayısını sınırlamaktadır. Bu bildiride, 19.09.2006-30.01.2007 tarihleri arasında merkezimizde intravenöz (IV) rekombinan doku plazminojen aktivatörü (rt-PA) verilen 8 kadın, 13 erkek toplam 21 akut iskemik inme olgusu sunulmaktadır. Olguların nörolojik durumları tedavi verilmeden hemen önce, yirmi dördüncü saatte, birinci hafta ve üçüncü ayda yapılan "The

National Institutes of Health Stroke Scale" (NIHSS) ile değerlendirilmiştir. Olguların yaklaşık üçte ikisinde ilk saatler ve ilk gün içinde belirgin klinik düzelme izlenmiş, bu düzelmenin 1. ve 3.ayda da devam ettiği gözlenmiştir. Sadece bir olguda tedaviye bağlı olduğu düşünülen semptomatik intrakranyal kanama gelişmiştir. Bir olgu kanama olmaksızın erken dönemde inmeye bağlı ödem artışı nedeniyle, bir olgu subakut, bir olgu da kronik dönemde nörolojik nedenler dışında sistemik nedenlerle kaybedilmiştir. Az sayıda olguyu içerse de bu sonuçlarla, iyi seçilmiş hastalarda IV rt-PA tedavisinin etkin ve güvenilir olduğu doğrulanmıştır.

Anahtar Kelimeler: Akut iskemik inme, trombolitik tedavi

INTRODUCTION

Acute ischemic stroke (AIS) is the third leading cause of death after coronary artery diseases and cancer in developed countries[34]. It has the highest morbidity ratios. Lots of people has cognitive, motor and sensory decline because of AIS. Cerebrum's vascularization is provided mainly from main cerebral arteries (anterior, middle, posterior) besides collaterals. In the occlusions of main vascular structures, there is a core generally defined as a part of the ischemic region that is irreversibly injured. Permanent deterioration occurs at the core within minutes. The peripheral regions are structurely and functionaly normal because of collateralization. Between the core and periphery there is a region called 'penumbra' which is the area of brain that is underperfused and is in danger of infarcting. The amount of collateral flow determines the size of the core and the penumbra. If the occlusion is not removed, the core size usually increases, while the salvageable penumbra decreases with time. The rate of change in the size of the core and the penumbra depends on the blood flow provided by the collaterals. The goal in the first hours after the onset of acute stroke is to prevent infarction and minimize the degree of permanent brain injury. In recent years, with the usage of the thrombolytic agents like streptokinase, urokinase and rt-PA in clinical practice, the intravenous and selective intraarterial thrombolytic treatment studies targeting the recanalization of thrombosed and/or embolised vascular structures are introduced. The benefical effect of rt-PA given to AIS patients within 3 hours of symptom onset is demonstrated in placebo controlled randomized trials[5,6,14,15,28] But it has limitations in AIS treatment since 3 hours treatment period is narrow and the effect of treatment is obtained by objective-subjective tests (like long term cure in disability scales, decreasing the death ratio..) in a latent period. In addition, higher dosages of IV rtPA is needed in AIS than in myocardial infarction (MI) for an effective treatment and there is a high risk of intracranial hemorrhage in AIS patients treated with IV rtPA. Several stroke patients due to emboli from proximal extracranial arteries or heart are old-hard and these kind of occlusions are resistant to thrombolytic treatment.[25,31] Despite these disadvantages, the value of IV rtPA is obvious. Declaration of the experiences of the stroke centers, will be helpfull in becoming widesprad of this treatment throughout the country. In this manuscript, the data of 21 patients with stroke who were treated with thrombolytic treatment in our department is discussed.

METHODS

This study evaluated 21 patients with acute ischemic stroke who received IV rt-PA within 3 h of symptom onset enrolled in our clinic between september 2006 and january 2008. The AIS patients who were awaken with deficits or in whom time of stroke onset was uncertain were excluded. Deficits of the patients were measured on the NIHSS. Patients with minor or significantly improving deficits (NIHSS<4) and the ones who were badly off on admission (NIHSS>22) were

excluded for thrombolytic therapy. Relatives of the patients within 3 hours of stroke onset were informed. Contraindications were evaluated (Table 1).Complete blood count, blood glucose level, coagulation profile (activated partial thromboplastin time (aptt), prothrombin time (pt) , International normalized ratio (INR)), liver and kidney function tests, electrolyte levels and chest X-rays were checked before rt-PA treatment. Patients were excluded if pretreatment head computed tomography (CT) showed signs of hemorrhage or major early infarction (diffuse sulcal effacement, poor differentiation between gray and white matter, diffuse hypodensity, hyperdense middle cerebral artery (MCA) sign, obscuration of lentiform nucleus, loss of the insular ribbon) involving more than one-third of the MCA territory. Before the procedure, types of blood of the patients were detected and erytrocyte suspensions and fresh frozen plasmas were prepared. Thrombolytic therapy (IV rt-PA) was given in a dosage of 0.9 mg./kg. (max. 90 mg.), %10 of total dosage in a loading dose, the rest in 2 hours via intravenous infusion. The vital signs and neurological examinations of the patients were followed in a period of 15 minutes within 2 hours, 30 minutes within 6 hours and 1 hour within 16 hours in 24 hours. Antiplatelet, anticoagulant therapy and arterial interventions had not applied to the patients within 24 hours of the procedure. Head CT scans were taken after 24 hours of the therapy. Neurological examinations were evaluated before the treatment, at 1 hour, at 24 hour, at 1 week and at 3 months.

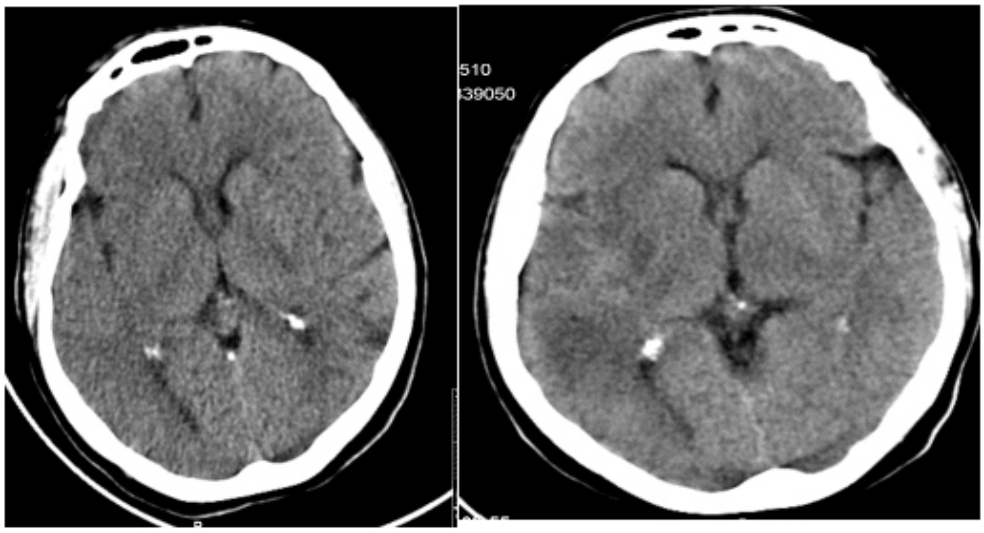
RESULTS

Patients

Twenty-one cases between the ages of 43-80 (mean age 63.86±10,83) recieved IV rt-PA therapy. Thirteen of them were male, 8 of them were female. 13 patients had large-artery atherosclerosis, 3 had cardioembolic stroke, 2 had small-vessel occlusion and 3 had stroke of undetermined etiology.

The findings of lab., CT and MRI

All of the laboratory investigations of the patients were normal. CT scans of 9 patients had early infarct signs. The head CT scans of a patient with cardioembolic stroke before and after the therapy were shown in figure 1.



1A 1B

Figure 1: *63 years old female patient with atrial fibrillation had disartria, anosognosia, left hemiparesia one day after cardioversion. NIHSS; before treatment:13 at first day:4 at 7th day:1 at 90th day: 0 A: Head CT scan before treatment (no pathological finding) B: Head CT scan at 24th hour (small pachy infarcts at MCA territory)*

Table 1: The indications and contraindications of IV rt-PA treatment in AIS patients (3,7,18,21)

Indications

Ischemic stroke within 3 hours of syptom onset
Measurable neurologic deficit
Exclusion of intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH)

Contraindications

Recent intracranial surgery or serious head trauma or recent previous stroke (in last 3 months)
ICH on CT or by history
Uncontrolled hypertension at time of treatment (e.g., >185 mmHg systolic or >105 mmHg diastolic)
Suspicion of SAH despite negative head CT
Seizure at the onset of stroke
Rapidly improving minor or major stroke (i.e., transient ischemic attack)
Active internal bleeding (e.g., gastrointestinal, urinary) within 21 days
Lumbar puncture within 7 days, major surgery within 14 days
Known bleeding diathesis, including but not limited to:
Current use of oral anticoagulants (e.g., warafin sodium)
with prothrombin time >15 s
Administration of heparin within 48 h. preceding the onset of stroke
and have an elevated activated partial thromboplastin time at presentation
Platelet count over 100,000/mm^3, thrombocyte count below 100.000/mm^3
Early hypodensity exceeding 1/3 of MCA territory

Table 2: The NIHSS of patients baseline, at 1 day, at 1 week and at 3 months.

Patient	NIHSS			
	Baseline	Day 1	Day 7	Day 90
S.K.	14	6	3	0
K.S.	4	3	2	1
B.A.	13	4	1	0
M.K.	20	20	10	6
V.Ü.	16	16	8	3
Ö.Ü.	17	17	14	7
K.C.	17	11- 24º	12	8
E.G.	19	11	9	5
D.A.	21	10	6	2
F.K.	11	3	1	0
A.E.	10	7	3	0
N.H.	9	2	1	0
E.K.	16	8	6	3
N.Y.	13	6	5	*
E.D.	10	0	0	*
H.T.	5	5	1	*
SK	11	11	6	*
FKA	17	16	16	***
Ş.Ç.	17	29	**	
H.H	13	8	**	
M.G.	21	21	21	***

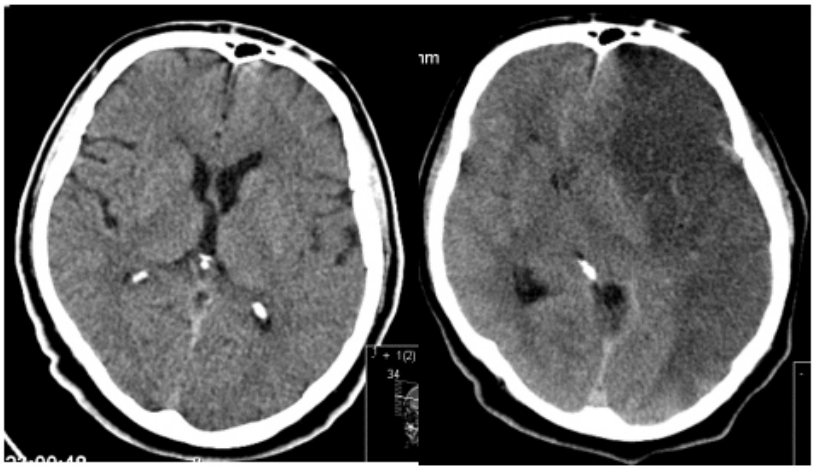
º The NIHSS of the patient at 28th hour.
* Not done yet
** Died within 7 days of stroke onset.
*** Died within 3 months of stroke onset

Neurological findings and thrombolysis

The patients' National Institutes of Health [NIH] Stroke Scale scores were between 4-21 (mean 14.0±4.8) Treatment windows of the patients were between 40 and 180 minutes (mean 151.25±35.6 min.) of stroke onset. 15 of the 21 patients (%71) had improved dramatically within one month of therapy (minimum 4 points decrease in NIHSS). 8 of them (%53) had improved within one hour. The NIHSS of baseline, at 1 day, at 1 week and at 3 months were shown in table 2.

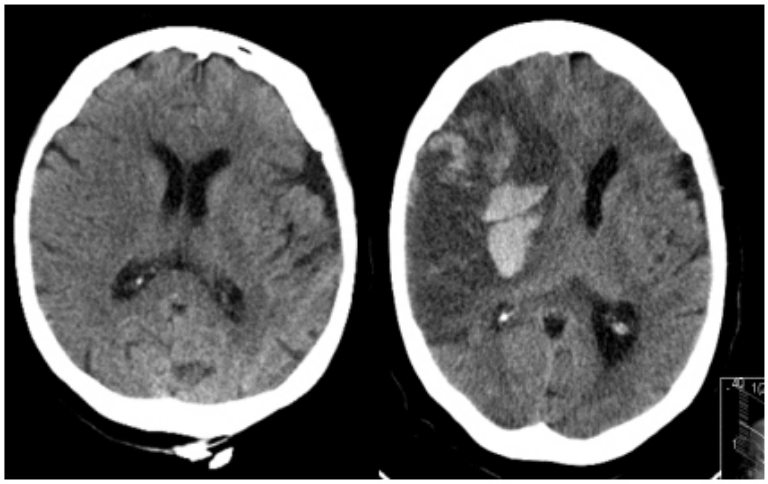
Complications

There was epistaxis in one patient within 24 hours of treatment. Four days after stroke one patient died because of brain edema and 13 days after stroke one patient died because of intracerebral hemorrhage. CT images of these patients were shown in figures **2** and **3**. We also lost 2 more patients, one at 5 days after, one at 49 days after the stroke with the causes of pulmoner thromboemboli and systemic infection, respectively.



2A 2B

Figure 2: *63 years old male patient had acute right hemiparesia and aphasia. NIHSS before treatment:17 at 24th hour:29. He died because of brain edema four days after treatment. A: Head CT scan before treatment (no pathological finding) B: Head CT scan at 24th hour (large infarct at left mCA territory and midline shift)*



3A 3B

Figure 3: *68 years old female patient had acute right hemiparesia. NIHSS; before treatment:21 at 24th hour:21 She died at 13 th. day A: Head CT scan before treatment (effacement of sulci at right MCA territory) B: Head CT scan at 24th hour (hemorrhage in the infarct at left mCA territory)*

DISCUSSION

Cerebral pathophysiological functions of the patients with AIS mostly depend on time of symptom onset and medical histories of each patient. Treatment specifically for core is not possible. Besides this, because of reperfusion ischemia, the risk of hemorrhagic transformation of the infarcted area is increased[9]. The therapies in AIS are targetted to penumbra which is vulnarable but structuraly normal region taking 7-17 ml. blood per 100 gram brain. Today IVand/or IA thrombolytic therapy is the best treatment modality in AIS. In this treatment the most important problem is the accurate patient selection. The indications, contrindications and the protocols of IV rt-PA treatment are assessed by NINDS (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Sudy Group), ECASS I-II (The European Cooperative Acute Stroke Study), ATLANTIS A-B (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke) ve STARS (The Standard Treatment with Alteplase to Reverse Stroke study) studies[2,3,6,7,14,15,18,28] (Table 1) Placebo controlled, randomized trials show that IV rt-PA treatment is effective and reliable in AIS patients within 3 h. of symptom onset. This effectiveness is decreased if the treatment is given within 3-4,5h. of symptom onset and the protocols for the treatment of patients within 3-6 h. of stroke onset are doubtfull[1,4,11,27,30]. IV rt-PA protocol in AIS patients within 3 h. of symptom onset is licenced in USA after NINDS trial in 1996[28]. It's licenced in our country in 2006. So, today thrombolytic treatment is routinelly used in our daily practice. Because of serious complications, difficulties in accurate patient selection slow this treatment's avaliability. After the affirmative results of the trial testing the differences of effectiveness of IV rt-PA given in patients within 3 h. of stroke onset between the findings of daily practice usage and the findings of placebo controlled randomized trials, the encouragement of less experienced stroke centers is increased. At the end of the trial it is concluded that there are no differences between results of experienced and less experienced centers. So, this treatment should be supported[33]. Because of the affirmative results of this trial, it's expected that there will be increase in the number of stroke centers giving thrombolytic treatment to suitable stroke patients in their daily practices.

The exact time of stroke onset must be known for thrombolytic therapy. The earlier the therapy the higher the success and the lesser the complication ratio. Early recanalization effects the prognosis positively. [32]. It's not always possible to know the exact time of stroke onset. If the patients are conscious or not aphasic, it's easy to learn the time of symptom onset. But if the patient is comatous or aphasic, the time of stroke onset should be thought as the last time he or she is seen without symptoms. If the patient wakes up with symptoms, sleep time is the time of stroke onset. In a patient with progression, begining time of mild symptoms is the time of stroke onset. If the patient has transient ischemic attack (TIA), time of stroke onset should be thought as the beginning time of last attack. Also time of arrival to hospital, the evaluation period in emergency service and in radiology department, application of thrombolytic therapy and recanalization are all very important parameters in the treatment's success. The most difficult thing in this treatment is to decresase the time between the house and the hospital. For that reason informing the society about the importance of this situation in stroke is very vital. The transformation system just for the stroke patients must be established. In our institution IV rt-PA treatment is put into practice according to the NINDS criteria for stroke. Two of 21 patients were already in the hospital when they had stroke, the

other IV rt-PA received patients admitted to the emergency department within 30-120 minutes of stroke onset. The time between the entrance of the patient to hospital and time of recanalization as known as ‘door to needle' is very important. It's not easy to be successful in making this time under one hour. We have no doubt that when we become experienced, the problems will be solved more easily and we will be more successful to decrease the time of ‘door to needle'.

The widespread availability, low cost, and accuracy in detecting intracranial hemorrhage have led head computed tomography (CT) scanning to become the first-line diagnostic test for the emergency evaluation of acute stroke. Head CT scans can detect ischemic regions within 6 hours of stroke onset. The identification of ischemic brain tissue by CT not only defines regions likely to infarct, but also may predict outcome and response to intravenous or intraarterial thrombolytic therapy. In spite of the early infarct signs detected in our patients, all of them got well accept one hemorrhagic case. The hemorrhagic AIS patient was the one with the highest NIHSS score in the group. Just by looking early infarct signs, the patient should not be excluded for IV rt-PA therapy if the other contraindications are not exist.

The risks of IV rt-PA treatment are increased if the patient is old with severe neurologic deficit, hypertension (HT), diabetes mellitus (DM) and early infarct signs on head CT scanning. The risk of hemorrhagic transformation in patients with NIHSS ≥20 and <10 are 17% and 3%, respectively. And this risk is increased if there are early infarct signs, hypodensity involving 1/3 of middle cerebral artery (MCA) territory, treatment window more than 3 h. of stroke onset .[19,20,29]. The initial NIHSS scores of 21 patients were between 4-21 (mean 14.0±4.8) 15 of 21 patients (%71) showed good prognosis within 3 months (at least 4 points decrease in NIHSS). Four of 21 patients died. One of these cases who show bad prognosis died because of intracranial hemorrhage. Intracerebral hemorrhage is the most serious complication in IV rt-PA therapy. This ratio is similar with the ones (%5.4-6.4) found in metaanalyses and randomized, controlled studies.[13,28] The patient was not very old and had no systemic disease like HT, DM. The NIHSS score was high (before treatment NIHS:22) In his head CT scanning in the right MCA territory there were effacement of sulci and gray-white matter zone differentiation and external capsule's margins were not clear. Some of other patients also had at least one early infarct sign but there were no complications causing bad prognosis. The difference in the patient with intracranial hemorrhage is his high NIHSS on admission. It should also be in mind that nothing really can be done in a case with large territorial infarct.

The main target in thrombolytic therapy is to create recanalization to confine the infarcted area. According to evidence based medicine; IV rt-PA must be given in an indicated patient within 3 h. of stroke onset. Our experience also supports this statement. More attention must be paid in patients with high NIHSS. Treatment decision must be made according to the patients' situations and the possible outcomes of the treatment must be explained to the relatives of the patients.

In conclusion, in patients with suitable indications IV rt-PA therapy is reliable and acceptable treatment in AIS. Very few amount of people have chance of reaching this therapy. Because of narrow therapetic index and high complication risks and the need of specialized centers lower the number of patients reaching this therapy. We need more stroke centers in our country. Since time is very important in thrombolytic therapy we have to make better multidiciplinary organizations. Cooperation between the centers is very important to make things better.

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