



# Repeated Intravenous Thrombolytic Treatment Experience with Tissue Plasminogen Activator in Patients with Acute Ischemic Stroke: Case series

## Akut İskemik İnme Hastalarında Doku Plazminojen Aktivatörü ile Tekrarlayan İntravenöz Trombolitik Tedavi Deneyimleri: Olgu Serisi

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### ABSTRACT

Ischemic stroke treatment has been changing in recent years and these procedures have positive effects on patients' prognosis, morbidity, and mortality. Intravenous Treatment with Recombinant Tissue-Type Plasminogen Activator (iv r-tPA) is one of the most efficient approaches in ischemic stroke patients. When administered in the first 4.5 h from symptom onset, it has been proven to be effective in functional improvement. However, physicians may feel hesitant about administering these treatments regarding the possible complications, especially the patients with recurrent stroke. The aim of this article is to contribute to the literature on the efficacy and safety of recurrent iv r-tPA therapy in patients with recurrent stroke. We present seven patients who underwent thrombolytic treatment more than one time between September 2017 and September 2020 and recorded the patients' gender, risk factors, age, initial/final National Institutes of Health Stroke Scale (NIHSS), and hemorrhagic transformation rates. Mean interval of iv r-tPA treatment was 244.7 days (minimum 58 days, maximum 1 year 9 months 10 days). Average of NIHSS calculated as 7.57 before the first and 8.26 before the second iv r-tPA treatment; at the time of discharge mean of NIHSS was 1.57 and 2.8 respectively for five patients. Five of the patients have been identified as cardioembolic in aetiology. In two of our cases, clinical worsening was observed in the follow-ups after iv r-tPA. Our symptomatic intracranial hemorrhage rates were similar to the literature seen in one patient. Rates of bleeding were directly proportional with calculated HAS-BLED scores in patients who were started anticoagulation. Our complication rates were similar with literature and the prognosis of recurrent r-tPA was discovered to have a good prognosis in the first 3 months.

**Keywords:** HAS-BLED; Hemorrhagic transformation; Ischemic stroke; iv tpa.

### ÖZET

İskemik inme konusunda tedavi yöntemleri son yıllarda değişime uğramakta ve bu yöntemler hastaların prognoz ve sağkalımı üzerinde olumlu etki göstermektedir. Rekombinant doku plazminojen aktivatörü alteplazın (r-tPA) kullanıldığı intravenöz trombolitik tedavi bu yaklaşımlardan biridir. Semptom başlangıcından itibaren ilk 4,5 saatte uygulandığında hastaların fonksiyonel sonuçlarının iyileşmesinde etkili olduğu kanıtlanmıştır. Fakat hekimler bazı durumlarda gelişebilecek komplikasyonlar nedeniyle tereddütte kalabilmektedir. Tekrarlayan inme hastalarında bu komplikasyonların gelişme olasılığının yüksek olma düşüncesi, intravenöz r-tPA uygulaması konusunda şüphede bırakmaktadır. Bu yazının amacı, tekrarlayan iskemik inmelerde uygulanan intravenöz trombolitik tedavinin etkin-

liği ve güvenilirliğine dair literatüre katkı sağlamaktır. Çalışmada, Eylül 2017-Eylül 2020 tarihleri arasında yedi tane birden fazla r-tPA tedavisi uygulanan hasta sunuldu. Hastaların yaş, cinsiyet, inme risk faktörleri, başvuru/final "National Institutes of Health (NIH)" inme skorları ve hemorajik transformasyon oranları değerlendirildi. Trombolitik tedaviler arasında ortalama süre 244,7 gün (en az 58 gün, en fazla 1 yıl 9 ay 10 gün); başvurudaki ortalama NIH inme skoru ilk r-tPA öncesi 7,57, ikincisi öncesi 8,26 idi. Taburculuktaki ortalama NIH inme skoru ilk tPA sonrası 1,57, ikincisi sonrası 2,8 idi. Beş hastada inme etiolojisinde kardiyoembolik olay saptandı. İki hastamızda klinik kötüleşme izlendi. Semptomatik hemorajik transformasyon oranımız literatüre benzerdi, bir hastada görüldü. Kanama oranları, antikoagülan başlanan hastalarda hesaplanan HAS-BLED ile doğru orantılıydı. Hastalarımızda komplikasyon oranları literatüre benzer görüldü ve ilk üç ayda tekrarlayan trombolitik tedavilerin prognozları iyiydi.

**Anahtar sözcükler:** İskemik inme; intravenöz tPA; HAS-BLED; hemorajik transformasyon.

Ischemic stroke treatment has been changing in recent years and these procedures have positive effects on patients' prognosis, morbidity, and mortality. Intravenous Treatment with Recombinant Tissue-Type Plasminogen Activator (iv r-tPA) is one of the most efficient approaches in ischemic stroke patients. When administered in the first 4.5 h from symptom onset, it has been proven to be effective in functional improvement.<sup>[1]</sup> Indications, relative contraindications, and absolute contraindications are created according to guidelines. However, physicians may feel hesitant about administering these treatments regarding the possible complications, especially the patients with recurrent stroke. Symptomatic intracranial hemorrhage and death is the most feared complications of this treatment.<sup>[2]</sup> This may prove to be even harder to decide for the patients presenting with acute stroke and had iv tPA in the past. When studies examined, it is seen that this process is even more difficult during the first 3 months. There are no contraindications in the guidelines for administering recurrent thrombolytic therapy in recurrent stroke patients. Despite this, there are not enough publications and researches in the literature on the results of multiple thrombolytic therapy.

The aim of this article is to contribute to the literature on the efficacy and safety of recurrent IV r-tPA therapy in patients with recurrent stroke.

## Methods

In this article we present seven patients who underwent thrombolysis treatment more than one time between September 2017 and September 2020 among 463 acute ischemic stroke patients received tPA in our neurology department. National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) are used for neurological examination. Upon presentation to emergency department, cranial computed tomography (CT) and cranial-cervical CT angiography (CTA) scan were obtained, INR, hemogram,

and other biochemical tests were obtained.

Alteplase treatment in the appropriate patients according to guidelines; total dose 0.9 mg/kg was administered as a 10% bolus and the remaining dose as an infusion to be completed in 1 h. Routinely at 24 h after treatment or earlier when clinically suspected hemorrhagic transformation was evaluated by a control cranial CT. Electrocardiogram (ECG) and transthoracic echocardiography were performed to each patient with cardiology consultation. If necessary, transeophageal echocardiography (TEE) and/or rhythm holter were performed.

Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was used for aetiological classification and treatment planning. In addition, patients' bleeding risks were evaluated by the HAS-BLED (hypertension [HT], abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs, or alcohol) scoring system who started anticoagulation due to atrial fibrillation (AF). Patients are summarized at Tables 1 and 2.

## Case Report

**Case 1** – A 83-year-old woman without any risk factors came to emergency department with difficulty of speaking. Her NIHSS score was 7 and MRS was 2. No acute pathology was present in cranial CT or cranial and cervical CTA. There was no indication for mechanical thrombectomy. Intravenous thrombolytic therapy was applied 270 minutes from symptom onset. Treatment completed without any complications. At the 4<sup>th</sup> day of hospitalization, she was discharged with an NIHSS of 1 and mRS of 2.

Rhythm holter could not be applied during hospitalization and she accepted as "stroke of undetermined etiology" according to TOAST classification and antiaggregant therapy was given. After 154 days, she again came to emergency department with the right hemiparesis. NIHSS calculated as 8

**Table 1.** Summary of clinical findings of patients undergoing recurrent tPA

Patient	Age	Sex	Comorbidities	Toast classification
1	83	F	No comorbidities	Cardioembolism
2	64	M	Dysrhythmia	Cardioembolism
3	57	M	No comorbidities	Cardioembolism
4	64	M	DM, HT	Large artery atherosclerosis
5	68	M	No comorbidities	Undetermined aetiology
6	72	M	DM, HT	Cardioembolism
7	87	F	Congestive heart failure	Cardioembolism

**Table 2.** Summary of clinical findings of patients undergoing recurrent tPA

Patient	mRS	NIHSS (initial)	NIHSS (final)	IV tPA starting time (min)	Time between 1 <sup>st</sup> and 2 <sup>nd</sup> tPA	Hemorrhagic transformation	HAS-BLED
1	2	7	1	210	154 days	none	1
	2	8	1	134		none	3
2	0	13	2	Unknown	313 days	none	
	0	3	1	132		none	
3	0	5	1	185	58 days	none	2
	0	11	3	100		none	3
4	0	6	1	115	108 days	none	
	1	5	4	140		none	
5	0	17	2	5	61 days	none	
	1	15	3	110		yes	
6	0	6	4	215	469 days	none	2
	1	9	10	227		yes	4
7	0	2	1	225	550 days	none	1
	0	7	5	260		yes	3

and 134 minutes from the onset of complaints iv r-tPA applied to her and completed without any complications. AF detected in ECG examination with repeated cardiology consultation. Oral anticoagulant therapy was started. He was discharged as NIHSS of 1 and mRS of 2.

In the follow-up of the stroke outpatient clinic, the mRS was 2, at 3 months.

**Case 2** – A 64-year-old male patient with a known diagnosis of dysrhythmia was presented to hospital with sudden onset speech difficulty. Intracranial bleeding was excluded by cranial CT, NIHSS was calculated as 3. When he presented to our emergency department, an occlusive thrombus was present in his left MCA M2 on the CTA. He wasn't a thrombectomy candidate due to his low NIHSS score. IV r-tPA was started at 132 minutes after symptom onset. In his past medical history, we found out that he was admitted to another neurology clinic left sided weakness 131 days ago. His NIHSS was 10 at the time and he had thrombolysis and

mechanical thrombectomy for right middle cerebral artery (MCA) lower trunk thrombus. He was discharged NIHSS:2, mRS:0 with antiaggregant treatment.

Upon further investigation, he was found to have dilated cardiomyopathy and decreased ejection fraction (EF: %35) and oral anticoagulant treatment was started. He was discharged as NIHSS:1 and MRS: 1. In the follow-up of the stroke outpatient clinic, the mRS was 0 at 3 months.

**Case 3** – A 57-year-old male patient with no known risk factors was presented to our hospital with complaints of weakness and numbness in his right arm and leg. Two years ago, he underwent mechanical thrombectomy for left MCA m1 occlusion and discharged as MRS:0. At the time of hospital admission, NIHSS calculated as 5. No sign of cranial hemorrhage was detected in CT. On CTA, the left MCA M1 segment is occluded, endovascular intervention was not considered due to low NIHSS. IV r-tPA commenced at the 185 minutes after symptom onset, was completed without complica-

tions. With cardiological evaluation and TEE, thrombus was detected in the left atrial appendix and oral anticoagulant treatment was started. He discharged as NIHSS:1 and mRS:1. The patient was non-compliant to warfarin and was admitted to our hospital 58 days later with another ischemic stroke. In the emergency evaluation, the NIHSS score was calculated as 11 and the INR value was 1.34. There was no hemorrhage in cranial CT, leftM1 segment was evaluated as chronic occlusion and endovascular intervention was not considered. IV r-tPA, which was started at the 100<sup>th</sup> min of his symptoms, was completed without any complications. The patient was discharged with oral anticoagulant therapy as NIHSS: 3, mRS:1. In the follow-up of the stroke outpatient clinic, the mRS was 1 at 3 months.

**Case 4** – A 64-year-old male patient(mRS:0) with a known history of diabetes mellitus (DM), HT and ischemic stroke 6 years ago presented to the emergency department with symptoms of hypoesthesia and paresis in the left arm. Cranial CT and CTA were in normal range. NIHSS was calculated as 6. IV r-tPA, which was started 115 minutes after symptom onset, was completed without complications.

The patient was externalized as NIHSS:1, mRS:0 with anti-aggregant therapy. One hundred and eight days after discharge, the patient presented again with left hemiparesis and speech difficulties. There was no haemorrhage in cranial CT, and right ICA critical stenosis was detected in CTA. The right ICA stenosis was deemed suitable for elective stenting. NIHSS calculated as 5. IV r-tPA, which was started at the 140<sup>th</sup> min of his symptoms, was completed without complications. The patient was discharged with NIHSS:4, mRS:1. In the follow-up of the stroke outpatient clinic, the mRS was 0 at 3 months.

**Case 5** – A 68-year-old male patient (mRS:0) with no known risk factors was admitted to our hospital with impaired speech and right hemiparesis. There was no hemorrhage in cranial CT. CTA was in normal range. NIHSS calculated as 17.

IV TPA, which was started at the 75 minutes after his complaints, was completed without complications. He was discharged as mRS:1 and NIHSS: 2 with antiaggregant therapy. He was evaluated as a stroke of undetermined etiology according to the TOAST classification. 61 days later, the patient (MRS:1) presented again with the right hemiparesis. Cranial CT and CTA were in normal range. NIHSS calculated as 15. IV r-tPA was started at the 110<sup>th</sup> min of his symptoms, and no hemorrhage was observed in the control cranial CT exami-

nation at the 24<sup>th</sup> h. While being followed up with NIHSS 3, she had an epileptic seizure at the 5<sup>th</sup> h of treatment. Cranial CT of the patient was repeated due to the decrease in Glasgow coma scale. A large intraparenchymal hematoma was seen that opened into the lateral ventricle filled the fourth ventricle and shifted to the midline. He was intubated and decompression surgery was planned by neurosurgery. After surgery, he was transferred to the intensive care unit.

**Case 6** – A 72-year-old male patient (mRS:0) with a known diagnosis of HT and DM was admitted to the emergency department with the left hemiparesis. There was no bleeding in the cranial CT examination and CTA showed weak flow in the right MCA lower trunk. NIHSS calculates as 6 therefore; mechanical thrombectomy was not planned. IV r-tPA, which was started at the 215<sup>th</sup> min of his symptoms, was completed without any complications. Oral anticoagulant was prescribed due to the detection of AF and the patient was discharged as NIHSS:3, mRS:1. After 1 year, 3 months and 14 days, he was presented to the hospital with impaired speech and right hemiparesis. INR (1.0) was in ineffective range. There was no bleeding in the cranial CT examination, NIHSS calculated as 9, and IV r-tPA, which was started at the 227<sup>th</sup> min of his symptoms, was completed without any complications. In CTA, the left internal carotid artery and MCA M2 segment occlusion were observed and mechanical thrombectomy was performed. A new oral anticoagulant treatment was planned for the patient because of the history of irregular drug use. While the neurological state was stable, sulcal hemorrhage was observed on cranial CT, which was taken on the 2<sup>nd</sup> day. On the 6<sup>th</sup> day of hospitalization, the patient with acute respiratory distress secondary to pneumonia was intubated and transferred to the intensive care unit.

**Case 7** – An 87-year-old female patient (mRS:0) with a diagnosis of congestive heart failure came to the emergency department due to impaired speech. There was no bleeding on the cranial CT examination, right vertebral artery was occluded on the CTA Since the basilar artery was patent, mechanical thrombectomy was not considered. NIHSS calculated as 2, and IV r-TPA, which was started at the 225<sup>th</sup> min of his symptoms and completed without any complications. Oral anticoagulant was prescribed due to the detection of AF and the patient was discharged as NIHSS:1, mRS:0. After 1 year, 9 months, and 10 days, he came to the hospital with left sided weakness. His INR was ineffective with 1.1. There was no bleeding on the cranial CT examination, NIHSS cal-

culated as 7. Ivr-tPA was started 260 minutes after symptom onset. On the 24-hour routine plain CT, a right frontal intraparenchymal haemorrhage with a width of 19 mm was observed. On the 8th day of hospitalization, he was discharged as NIHSS: 5 and mRS: 1 with full resorption.

## Discussion

Of the seven patients included in this article, five of them were male and 2 of them were female. Mean interval of iv r-TPA treatment were 244.7 days (minimum 58 days, maximum 1 year 9 months 10 days). The mean NIHSS score was calculated as 7,57 before the first thrombolysis and 8,26 before the second one. At the time of discharge, the mean NIHSS score was 1,57 and 2,8 respectively for the first and second treatments for the 5 patients.

Since the other two patients were sent to the intensive care unit, they were not included in the study.

No complications were encountered during IV r-tPA administration in patients, all of them were treated and no allergic reaction was observed in any of them.

The cases were evaluated according to the TOAST classification. Atrial fibrillation found in 3 patients, 1 patient had dilated cardiomyopathy and 1 patient had left atrial appendix thrombus, a total of 5 patients with cardioembolic aetiology. Rhythm holter was recommended to the other 2 patients, but we were not able to obtain results. They were classified as stroke of undetermined etiology.

In two of our cases, clinical worsening was observed in the follow-ups after iv tPA.

68-year-old male patient who had clinical deterioration (initial NIHSS:15) underwent decompressive surgery due to an intraparenchymal hematoma that created a shift effect. Then he was transferred to the intensive care unit.

The 72-year-old male patient (initial NIHSS:9) was transferred to the intensive care unit because of an acute respiratory failure due to bacterial pneumonia. He had intraparenchymal haemorrhage however was completely stable from a neurological point of view. AF was found in the etiology and the HAS-BLED score was 4.

One of our patients, in whom we found asymptomatic hemorrhagic transformation in the follow-ups, was discharged after resorption of the hematoma. In this patient, the cardiac rhythm was AF and the HAS-BLED score calculated as 3.

Major bleeding rates in the studies were 4.1% in patients with HAS-BLED 2, 5.8% in patients with 3, and 8.9% in patients with a score of 4.<sup>[3]</sup> HAS-BLED score 3, 4, and 5 considered as high-risk groups for bleeding. In patients who started anticoagulation, we assessed the scores and determined that the risk of bleeding was directly related to the calculated values.

Cappellari et al. reported 5 patients who underwent recurrent thrombolytic therapy and one of them had symptomatic intracranial haemorrhage. Between tPAs applied before and after 3 months, there was no significant difference in the rate of bleeding. One symptomatic intracranial hemorrhage was reported in the case series of nine patients by Sauer et al.<sup>[5]</sup> In the case report of seven patients by Yoo et al.<sup>[6]</sup> and in the series of 24 patients by Laible et al.,<sup>[7]</sup> symptomatic intracranial hemorrhage was not observed.

In the case presented by Vanood et al.,<sup>[8]</sup> the patient who underwent r-tPA 2 times with an interval of 4 days was discharged as NIHSS 2. They mentioned four patients in the literature. When r-tPA was administered with a maximum interval of 4 days to them, there was one symptomatic bleeding observed. However, some of the patients received the second one at a lower dose. The case of Sposato et al.<sup>[9]</sup> with symptomatic bleeding and was treated at 0.9 ml/kg dose r-tPA at 4 days intervals.

In our case series with seven patients, symptomatic intracranial hemorrhage rates were similar to the literature. Two of our patients, IV r-tPA was applied in 3-month period (on the 58th and 61st days). Our first patient was discharged without any complications. In other patient, intraparenchymal hematoma was observed. In the clinical follow-ups, he was transferred to intensive care unit.

It was observed that the studies focused on the application of thrombolytic therapy especially in recurrent strokes. Successful results were obtained in the treatments applied in three months or earlier and the feared complications were observed at a low rate.<sup>[4,6,10]</sup>

In our article, we planned to evaluate the risk of bleeding in IV r-tPA patients using the HAS-BLED scoring system. Considering the scores, the risk was found to be directly proportional to the values calculated in the patients who started anticoagulation. The literature on this subject have not yielded any data and we believe that additional clinical experience and research will lead to more reliable findings.



In the literature, recurrent r-tPA treatment was evaluated to yield good functional outcome first three months. Complication rates of recurrent application in our case series are similar when compared with other studies.

### Disclosures

**Informed consent:** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – I.S., I.K.A.; Design – K.G.K., I.S.; Supervision – E.G., P.D.A.; Materials – K.G.K.; Data collection &/or processing – Ç.İ.Ö.B., K.G.K.; Analysis and/or interpretation – I.K.A., P.D.A.; Literature search – K.G.K.; Writing – K.G.K., Ç.İ.Ö.B.; Critical review – I.K.A.

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