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ORIGINAL ARTICLE **ARAŞTIRMA YAZISI**

PROGRESSIVE ISCHEMIC STROKE:
CLINICAL FEATURES AND EVALUATION OF SHORT- AND LONG-TERM TIROFIBAN THERAPY

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ABSTRACT

OBJECTIVE: Progressive ischemic stroke is a disorder frequently seen in neurological intensive care unit and stroke units. The purpose of this retrospective study was to evaluate the clinical features of progressive ischemic stroke patients in neurological intensive care unit, the short- and long-term efficacy of tirofiban therapy, and the adverse events observed.
METHODS: The study included patients with minor-moderate progressive ischemic stroke diagnosed in the period between January and December 2014. The National Institute of Health Stroke Scale scores at 24 hours after tirofiban therapy and on discharge, and the modified Rankin score and Barthel Index value at the end of the 3. month were recorded from the patients' files.
RESULTS: The study included a total of 28 patients, 15 (53.6%) of whom were males. The mean age of the cases was 65.36±11.32 (39-80). According to the TOAST classification, 10 cases had large vessel atherosclerosis, 9 had cardioembolism, and 9 had small vessel disease. When the groups were evaluated in terms of stroke subtypes, the NIHSS score was highest in the cardioembolic group and lowest in the small vessel disease group. The cases in the small vessel disease group demonstrated the most marked fall in NIHSS score.
CONCLUSION: Tirofiban may be an alternative therapy for progressive ischemic stroke in case of proper selection of patients and under proper monitorization to detect side effects.
Keywords: Barthel index, progressive ischemic stroke, Tirofiban.

PROGRESİF İSKEMİK İNME: KLİNİK ÖZELLİKLER VE TİROFİBAN TEDAVİSİNİN KISA VE UZUN DÖNEM ETKİNLİĞİNİN DEĞERLENDİRİLMESİ

ÖZET

AMAÇ: Progresif iskemik inme nörolojik yoğun bakım ve inme ünitelerinde sıklıkla karşılaşılan bir klinik durumdur. Retrospektif olarak planlanan bu çalışmanın amacı progresif iskemik inmenin klinik özelliklerinin, tirofiban tedavisinin kısa ve uzun dönem etkinliğinin ve komplikasyonların değerlendirilmesidir.
GEREÇ ve YÖNTEM: Ocak 2014-Aralık 2014 tarihleri arasında hafif ve orta şiddetli progresif iskemik inme tanısı alan hastalar çalışmaya alınmıştır. Hastaların dosya bilgilerinden tirofiban tedavisi ve taburculuk esnasında NIHSS skoru, 3. ayda ise modifiye Rankin skoru ve Barthel indeksi değerleri hesaplanmıştır.
BULGULAR: Yirmi sekiz hastadan oluşan çalışmada 15 hasta(% 53,6) kadın idi. Hastaların yaş ortalaması 65,36 ± 11,32 (39-80) idi. TOAST sınıflamasına göre inme etiyolojileri 10 hastada büyük arter aterosklerozu, 9 hastada kardiyoembolizm ve 9 hastada küçük damar hastalığı olarak belirlendi. İnme etiyolojilerine göre değerlendirildiğinde NIHSS skoru kardiyoembolizm grubunda en yüksek iken küçük damar hastalığı grubunda en düşük olarak hesaplandı. Etiyolojide küçük damar hastalığı olan olgularda tedavi sonrası NIHSS skorundaki düşme en fazla olarak belirlendi.
SONUÇ: Progresif iskemik inme hastalarında uygun hasta ve yan etkilerin dikkatli takibi ile tirofiban iyi bir tedavi alternatifi olabilir.
Anahtar Sözcükler: Barthel indeksi, progresif iskemik inme, Tirofiban.

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INTRODUCTION

Following the onset of various therapies in cases with acute ischemic stroke, some patients may show a regression in their neurological status (1-3). Progressive ischemic stroke (PIS) is a clinical picture frequently encountered in neurological intensive care unit (NICU) and stroke units with no consensus on its therapy which distresses the clinician. The therapy for acute ischemic stroke, being applied for about 20 years and approved by the Food and Drug Administration (FDA), is intravenous tissue plasminogen activator (tPA) (4).

In recent years, endovascular interventions providing significant recanalization in selected appropriate patients have gained increasing popularity. However, the presence of many cases contraindicated for thrombolytic and endovascular therapy and the presence of progressive cases despite medical therapy render patient management quite difficult. For such cases, different therapeutic approaches have been suggested, one of which is tirofiban therapy. Although only small series of cases have been studied, reports have shown that tirofiban could be an appropriate alternative for the therapy of progressive stroke in appropriately selected patients.

Glycoprotein (gp) IIb/IIIa receptor inhibitors, which are highly selective platelet antagonists, effectively prevent platelet aggregation by reversibly blocking fibrin-binding receptors (5). It has been shown that in experimental stroke models, gp IIb/IIIa receptor inhibitors reduce the infarct volume, even in delayed therapy (6, 7).

Tirofiban is a highly selective gp IIb/IIIa receptor inhibitör, which has a rapid onset and short duration of action after administration. Its use has been approved by FDA, even in cases of acute coronary syndrome of over 48 hours. Pilot studies on small case groups have reported that tirobifan prevents cerebral microembolism in cases with acute ischemic stroke or with symptomatic carotis lesion, and also reduces the infarct area as demonstrated by diffusion and magnetic resonance imaging (MRI) (8).

The purpose of this study was to determine the clinical features of PIS patients in department of neurology and NICU and the short- and long-term efficacy of the applied tirofiban therapy.

MATERIAL AND METHODS

This retrospective study was performed on patients hospitalized in our center with the diagnosis of acute ischemic stroke in the period between January and December 2014. The criteria for inclusion in the study were: presence of minor or medium-degree stroke on admission [with National Institute of Health Stroke Scale (NIHSS) score of 2-18], final diagnosis of PIS, age range of 18-80, contraindication for thrombolytic therapy, tirofiban use for therapy, and reachable control data at the end of the 3. month. The criteria for exclusion from the study were history of cerebral or extracerebral hemorrhage, known intracranial disease (such as arteriovenous malformation, neoplasm, aneurysm), liver disease, thrombocytopenia (platelet number <100.000), platelet dysfunction, major trauma, major surgery in the last 3 months, and past stroke; coagulopathy [prothrombin time (PT) >1.3 times of the normal and international normalized ratio (INR) >1.3].

The patients hospitalized with the diagnosis of acute ischemic stroke and demonstrating an increase of ≥2 in NIHSS score during their follow-up then received the final diagnosis of progressive ischemic stroke after excluding hemorrhagic transformation or intracerebral hemorrhage by cerebral computed tomography (CT) and diffusion MRI scans.

The following features of the patients were documented: Age, gender, at what hour of stroke the progression appeared, NIHSS score on admission, NIHSS score after progression, NIHSS scores at hour 24 after tirofiban therapy and on discharge, modified Rankin score (mRS) after 3 months, Barthel index (BI) on discharge and after 3 months, localization of the infarct by cerebral CT without constrast or diffusion-weighted MRI scans, stroke topography, stroke subtype classification using the TOAST (Trial of Org 10172 in acute stroke treatment) criteria, hypertension, diabetes mellitus, active smoking, hyperlipidemia, coronary artery disease, congestive heart failure, presence of atrial fibrillation, and complications after tirofiban therapy such as intracerebral hemorrhage, hemorrhagic transformation in the infarct, peripheral hemorrhage, genitourinary system (GUS) or gastrointestinal system (GIS) hemorrhage. Furthermore, the results of the following examinations were documented;

Diffusion-weighted MRI and cerebral CT scans, color doppler ultrasonography and/or cervical MR angiography of the carotis and vertebral artery, transthoracic echocardiography (ECHO), electrocardiography (ECG), and all examinations to determine the etiology of "young stroke" in patients under age 55 (transesophageal ECHO, 24-hour Holter ECG monitoring). Intracranial vascular structures were evaluated with cerebral MR angiography in patients with the suspect of major vessel occlusion.

As in the treatment of acute coronary syndrome, with unfractionated heparin 500 U/h, tirofiban (Agrastat®, Merck & Co., Inc., Whitehouse Station, NJ, USA) at a dose of 0.4 µg/kg/min was administered within 30 minutes and at a dose of 0.1 µg/kg/min as continuous infusion within 48 hours. Thereafter, the treatment was continued with antithrombotic or anticoagulant therapy according to the etiology of stroke.

Prior to the study, the study plan was approved by the local Ethics Committee (date: 9 January 2016; meeting number: 49; decision number: 21).

Statistical Analysis: All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. For comparison of two related(paired) continuous variables, Wilcoxon Signed Rank test was used. To evaluate the change in the NIHSS and Barthel index measurements obtained in the time interval, the Repeated Measurements Analysis was applied. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

In total, 510 consecutive patients with acute ischemic stroke admitted to department of Neurology and intensive care unit were evaluated for PIS. Twenty-eight of them diagnosed as PIS and treated with tirofiban were included to the study. The patients were selected from the patient files of the Outpatient Clinic for Cerebrovascular Diseases. Of the patients, 15 (53.6%) were males, and the mean of the stroke age was 65.36±11.32 (39-80). According to the TOAST classification, 10 patients had large vessel atherosclerosis, 9 had cardioembolism, and 9 had small vessel disease. Topographically, 18 cases had only anterior circulation, 8 cases had only posterior circulation, and 2 cases had anterior + posterior circulation infarct. Major vessel occlusion in medial cerebral artery (M2 segment) was determined in 3 patients with Cerebral MR angiography. Acute infarct was localized in the cortex in 12 cases, in the basal ganglia in 7 cases, in the brainstem in 5 cases, in the cortex + brainstem in 2 cases, in the basal ganglia + brain stem in 1 case, in the brain stem + cerebellum in 1 case (Table 1).

Table 1. Vascular risk factors, clinical features, and adverse events in patients with progressive ischemic stroke.

	n	%
Vascular risk factors		
Hypertension	18	64.3
Diabetes Mellitus	13	46.4
Active smoking	8	28.6
Hyperlipidemia	4	14.3
Heart disease	13	46.4
Stroke subtype		
Large vessel disease	10	35.7
Small vessel disease	9	32.1
Cardioembolism	9	32.1
Infarct localization		
Cortical	12	42.8
Basal Ganglia	8	28.5
Brainstem	5	17.8
Cortical and brainstem	1	3.6
Basal ganglia and brainstem	1	3.6
Brainstem and cerebellum	1	3.6
Stroke topography		
Anterior circulation infarct	18	64.3
Posterior circulation infarct	8	28.6
Anterior + posterior circulation infarct	2	7.1
Adverse Events		
Symptomatic intracerebral hemorrhage	0	0
Hemorrrhagic transformation	1	3.6
Gastrointestinal system hemorrhage	0	0
Genitourinary system hemorrhage	2	7.2
Peripheral hemorrhage	0	0
Thrombocytopenia	0	0

The progression occured on average 27.85 hours (6-72 hours) after the onset of stroke symptoms. The average NIHSS score at hour 1 of admission was 7.14 (2-6); the score at the time of progression occurence was 10.21 (5-21) with an average NIHSS increase of 3.07 (2- 11); at 24 hours after administration of tirofiban, the score was 9.79 (3-19), and on discharge the score was 9.46 (1-18) (Figure 1).

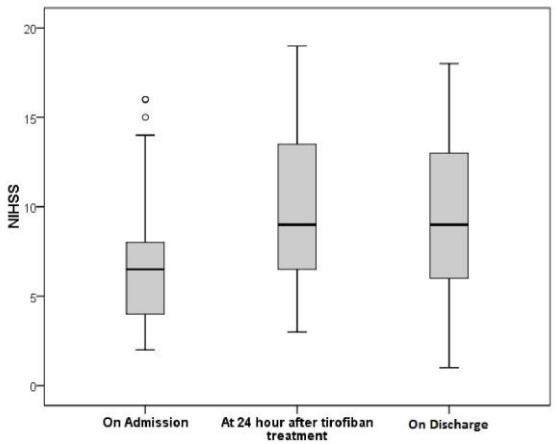

Figure I. Changes in NIHSS values on admission, at 24 hours after tirofiban treatment, and on discharge.

In the evaluation of the patient groups in terms of stroke subtypes, the NIHSS score was found to be highest in the cardioembolic stroke group and lowest in the small vessel disease group. The changes in the NIHSS score during therapy were not significant in either of the three groups ($p>0.05$), but the NIHSS score decreased mostly in the small vessel disease group. When all cases were evaluated, there was no significant change in the NIHSS score in the acute stage after therapy (Figure 2).

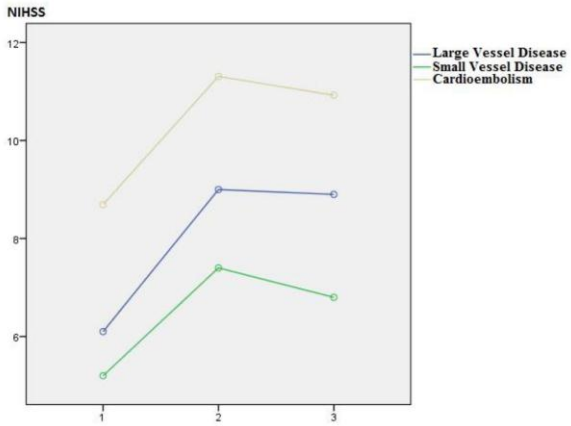

Figure II. NIHSS changes in the acute stage of therapy in stroke subtypes (1. Before therapy, 2. At 24 hours after therapy, 3. On discharge).

The mean of BI on discharge was calculated as 65.00±22.66 and at the end of the 3. month as 77.41±24.07, which were statistically significant ($p<0.01$). However, the lowest BI at the end of the 3. month was found in the cardioembolic stroke group. When the mean BI values on discharge and at the end of the 3. month were evaluated in terms of stroke etiology, they were found to be 62.22±18.21 and 79.44±17.93 ($p<0.04$), respectively, in the large vessel atherosclerosis group; 68.00±16.80 and 85.00±19.68 ($p<0.04$), respectively, in the small vessel disease group, and 65.77±28.05 and 73.08±29.40 ($p<0.04$), respectively, in the cardioembolism group. The BI values found in all three groups were significant just at the limit (Figure 3).

The mRS at the end of the 3. month was assessed in all three groups. It was found to be 0-2 in 14 cases, 3-4 in 10 cases, and 5 in 4 cases. Parallel to BI, mRS was high in the cardioembolic stroke group and low in the small vessel disease group.

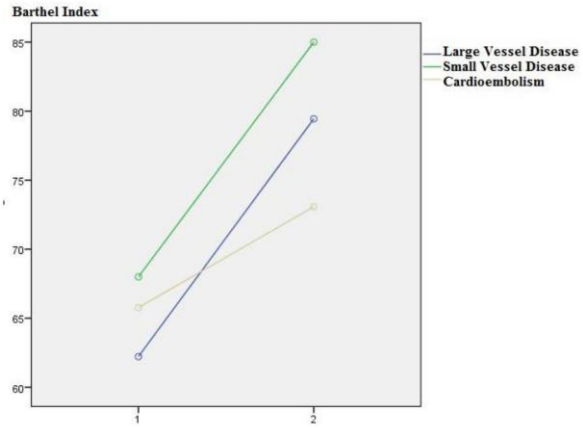

Figure III. Short- and long-term changes in Barthel Index in stroke subtypes (1. On discharge, 2. At the end of month 3).

DISCUSSION

Acute ischemic stroke is a clinical entity widespread all over the world with significant high rates of mortality and morbidity. Thrombolytic therapy with tPA carried out in an appropriate therapeutic window is an effective therapy approved by FDA, but only less than 2% of the cases are treated with tPA (9). Furthermore, if the parameters of the therapeutic window for thrombolytic therapy are not determined or if there are contraindications, the standard medical therapies are administered.

Tirofiban, the gp IIb/IIIa antagonist, used for the therapy of acute coronary syndrome leads to hemorrhagic complications less frequently than thrombolytic drugs. In the present study, tirofiban

was administered to patients who did not have thrombolytic therapy, showed progression at least 6 hours after the onset of stroke symptoms, and were diagnosed as progressive stroke.

A SaTIS study comparing tirofiban with placebo on patients with NIHSS score of 4-18 has reported the average time length between the onset of symptoms and progression as 9.25 hours, whereas in our study, the mentioned average time length was determined as 27.85 hours (10). In the SaTIS study , the reliability and efficacy of tirofiban compared to placebo were assessed, but the early and long-term efficacy of the drug according to stroke subgroups were not evaluated (10). As result, the study reported that tirofiban was not very effective in the early stage of stroke, but the mortality rate in the 5-month follow-up was low with tirofiban therapy, when compared to other therapies (10).

An evaluating preliminary study that included two patient groups which received Tirofiban + alteplase or only alteplase treatment has reported that when study group received tirofiban + alteplase treatment was compared to the study group which received only alteplase treatment, safe, feasible and potentially efficacious with improved outcomes were observed in study group which received tirofiban + alteplase treatment (11). In an another study which compared Tirofiban monotherapy, trombolytic treatment and interventional treatment, bleeding complication was not observed in tirofiban group but recanalization rate was found lowly (25%) compared to other groups (12).

Intra arterial thrombus formation is promoted by the activation of the trombotic pathomechanism that is activated after endothelial damage for instance in rupture of an arteriosclerotic plaque, and in arterial thromboembolism (13). Thus, the target of gpIIb/IIIa antagonists is not thrombolysis and arterial recanalization, but the prevention of arterial reocclusion (14). As a consequence, thrombolytics have been combined with gpIIb/IIIa inhibitors in acute cerebral ischemia both in animal models and in human stroke (15,16).

In our study, we found no significant difference between the NIHSS scores before and at hour 24 after tirofiban use in all of our patients ($p>0.05$). However, the lowest and highest change in the NIHSS score were seen in the cardioembolic stroke group and in the small vessel disease group, respectively. But when the three groups were compared, there was no significant change in acute stage NIHSS score. The low change in the NIHSS score in the cardioembolism group was thought to be due to the higher NIHSS score at the onset of stroke and to the larger infarct area in cardioembolic patients. In their study on tirofiban therapy of 35 patients with progressive stroke, Philips et al. determined the stroke subgroups as large vessel atherosclerosis and small vessel disease subgroups and reported a significant fall in the NIHSS scores 24 and 48 hours after tirobifan administration and after tirofiban infusion in the small vessel disease group (17). In our study, the highest change in the NIHSS score was determined in the small vessel disease group, but this change was statistically insignificant. This insignificance was related to the presence of fewer patients in this group.

The progression risk is greater in lacunar stroke, which is associated particularly with small vessel disease. This increased risk has been associated with lipohyalinosis, intracranial branch atherothrombosis and endothelial dysfunction, and progressive occlusion of small vessels (18-20). Tirofiban is thought to improve microcirculation by affecting these mechanisms (18).

When the patients' BI values on discharge and on 3. month after tirofiban were compared, there was a statistically significant increase in the values in all patients. When each of the three stroke subgroups was evaluated, a borderline significance was found in all groups. However, the BI values of large vessel atherosclerosis and small vessel disease groups showed the highest rise. These results led us to think that tirofiban therapy does not markedly improve the clinical picture in the acute stage, but may stop the progression of stroke; the results showed that functional improvement after tirofiban therapy is markedly better at the end of the 3. month than in the acute stage of stroke.

During therapy and hospitalization, hemorrhagic transformation of cerebral infarct occured in 1 patient and macroscopic hematuria occurred in 2 patients. The case with hemorrhagic transformation, which occured on the second day of therapy, was in the cardioembolic stroke group. The SaTIS study reported symptomatic intracerebral hemorrhage in 1.6% of the cases. In our study, symptomatic intracerebral hemorrhage did not occur in any of our patients (10). The macroscopic hematuria seen in two patients in the

first 24 hours of the therapy was associated with use of urinary catheter. A lower prevalence of macroscopic hematuria after tirofiban therapy was reported in patients with acute coronary syndrome (10). This lower prevalence is a normal finding since urinary catheters are less frequently used in acute coronary syndrome patients than in stroke patients (10). One of the major side effects seen in clinical cardiology studies with tirofiban is thrombocytopenia (20-23). During the follow-up of our cases, no symptomatic or asymptomatic thrombocytopenia occured.

The major complication determined in our study was hemorrhagic transformation, which was seen in a case with cardioembolic stroke. Special attention should be paid to this complication, particularly in patients with cardioembolic stroke treated with tirofiban. There was no mortality on admission or until the end of the 3-month follow-up among patients treated with tirofiban.

In conclusion, tirofiban treatment should be started as soon as progression is determined in patients with PIS and particularly in those with small vessel disease as the etiology of stroke. Such an approach would provide long-term functional improvement. The cases receiving tirofiban therapy should be followed-up for development of thrombocytopenia, hemorrhagic transformation of infarct, primary intracerebral hemorrhage, GIS and GUS bleeding, and peripheral hemorrhage.

Tirofiban therapy of PIS patients who cannot receive thrombolytic therapy or cannot undergo endovascular intervention shows relatively few major side effects and better improvement in patients' long-term mRS and BI scores. Therefore, tirofiban may be an alternative therapy for PIS in case of proper selection of patients and under proper monitorization to detect side- effects.

Limitations

The limitations of this study include being a retrospective study and limited number of patients included. A prospective study on a larger group of patients would provide more effective results.

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