Exp Biomed Res 2025; 8(1): 40-48 **https://doi.org/10.30714/j-ebr.2025.235**

Experimental Biomedical Research *Original article*

Comparison of acute ischemic stroke patients receiving thrombolytic therapy: Patients admitted to the emergency department direct and after telestroke thrombolytic therapy and those referred to thrombolytic therapy

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ABSTRACT

Aim: To evaluate treatment times and outcomes in patients receiving intravenous thrombolytic therapy via different protocols. This analysis focused on three distinct patient groups: those directly admitted to a central emergency department with suspected acute ischemic stroke, those brought to the stroke center by emergency services from other centers for thrombolytic therapy, and those receiving telestroke consultation-supported thrombolytic therapy before transfer.

Method: This retrospective study reviewed medical records of 198 acute ischemic stroke patients admitted to a tertiary hospital emergency department between January 1, 2017, and December 31, 2020. Demographic data, admission and treatment times, clinical outcomes (modified Rankin and National Institutes of Health Stroke Scale (NIHSS)), and three-month mortality rates were assessed.

Results: Common risk factors were hypertension, atherosclerosis, diabetes, and hyperlipidemia. Stroke etiology included large artery atherosclerosis and small vessel occlusion in 26.3% of cases, and cardioembolic stroke in 17.2%. Patients with higher modified Rankin scores also had significantly higher NIHSS. A significant reduction in modified Rankin scores was observed at the third month across patient groups, though no significant differences were found in recanalization times or third-month scores between groups.

Conclusion: The “drip and send” method for rapid transfer to stroke centers was shown to be critical in improving clinical outcomes, emphasizing the importance of early intervention in stroke prognosis. This study supports adopting the “drip and send” model as a standard stroke treatment approach.

Keywords: Acute ischemic stroke, drip and send, intravenous thrombolytic therapy, endovascular thrombectomy, functional outcome.

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Received: 2024-11-07 / Revisions: 2024-11-15

Accepted: 2024-11-19 / Published: 2025-01-01

1. Introduction

Stroke is a leading cause of mortality and disability worldwide [1]. Acute stroke ranks as the third most common cause of death, following heart disease and cancer, and it represents a significant source of morbidity and mortality both in Turkey and globally. Additionally, it is one of the leading causes of long-term disability in Europe [2-5].

Determining stroke etiology is crucial for managing risk factors, guiding treatment decisions, and predicting patient outcomes.

Ischemic strokes are primarily attributed to extensive artery atherosclerosis, cardioembolism, and small vessel disease [6]. In this context, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system remains the most widely utilized method for identifying the underlying cause of stroke [7]. Noncontrast brain computed tomography (CCT) should be performed rapidly in stroke diagnosis. This is critical to identify contraindications to fibrinolysis and to allow early fibrinolytic therapy. Alternatively, diffusion-weighted magnetic resonance imaging (MRI/DWI) is a superior diagnostic tool, providing high sensitivity (88–100%) and specificity (95–100%) in the early diagnosis of acute infarction [8,9].

The National Institutes of Health Stroke Scale (NIHSS) is the most commonly used scale to assess stroke severity in stroke patients. The NIHSS is administered within the first 10 minutes of the patient's presentation to the emergency department, helping to rapidly determine the neurological damage and etiology of stroke [10,11]. The Modified Rankin Scale (mRS) measures functional recovery after stroke; 0-2 points indicate independence, 3-5 points indicate dependency, and 6 points indicate death [12].

The primary goal of acute stroke treatment is to restore blood flow to ischemic brain tissue [13]. Recanalization and reperfusion of the occluded vessel can reduce the infarct size and improve neurological deficits [14]. Two basic evidence-based approaches are used: chemical thrombolysis with intravenous recombinant tissue plasminogen activator (IV tPA) and endovascular thrombectomy (EVT). Since the advent of IV t-PA therapy, patients with neurological symptoms related to acute ischemic stroke are brought to the nearest hospital designated as a stroke center by 112 teams. IV t-PA is a treatment that should be administered within 4.5 hours of the onset of symptoms, and its standard dose is 0.9 mg/kg [15]. However, many hospitals do not have a stroke center with specialists who can assist in timely treatment with IV tPA. In addition, many emergency physicians are reluctant to administer IV t-PA in a setting without a stroke team or appropriate neurological or neurosurgical resources because of the complications of t-PA. To overcome these problems, when IV t-PA is recommended, patients are first treated via telestroke consultation at their initial hospital to avoid wasting time. Then, they are transferred to a comprehensive stroke center for continued care and, if deemed appropriate, EVT treatment. This process of delivering IV t-PA to stroke patients in areas without a stroke center and then transporting them has been called the “drip and send” method. Early recanalization may improve patient outcomes by reducing occlusion-related mortality [16].

In this study, the time to treatment and clinical outcomes of patients who were directly admitted to the central emergency department with a preliminary diagnosis of acute ischemic stroke, referred to receive IV t-PA treatment via emergency health teams from an external center, and transferred to our stroke center after receiving IV t-PA treatment with telestroke support were compared. The study aimed to evaluate the effects of different delivery protocols on 3-month mortality and functional recovery of patients and emphasize the importance of early intervention in stroke management.

2. Materials and methods

2.1. Study design: Approval was granted by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee for this retrospective observational study (Decision No: 2021/95). In this study, we retrospectively analyzed patients

with acute ischemic stroke who presented to the Emergency Department of Bolu Abant İzzet Baysal University Training and Research Hospital and received IV t-PA treatment between January 1, 2017, and December 31, 2020.

This retrospective study included patients diagnosed with cerebrovascular disease, identified by the ICD code I167.9, who received intravenous tPA from the hospital's automated system. Patients younger than 18 years and those with incomplete data were excluded from analysis. The study examined various factors, including demographic information (age, gender, medical history), imaging findings, time of admission, time from symptom onset to arrival at the emergency department, time from symptom onset to administration of intravenous tPA, stroke etiology as classified by the TOAST system, and the modified Rankin Scale (mRS) scores at admission and after three months.

2.2. Groups: In our study, patients diagnosed with acute ischemic stroke who applied to the emergency department were divided into three groups:

1. Center Group: Patients taken from within the provincial borders via outpatient or Bolu 112 Emergency Health Services were directly applied to our hospital within 4.5 hours of the onset of symptoms and received IV t-PA treatment. After being evaluated by emergency physicians, these patients were directed to non-contrast CBT and MRI/DWI imaging. The on-call neurologist administered IV t-PA bolus and maintenance therapy at a standard dose (0.9 mg/kg) with the consent of the patients.

2. Transfer Group: Patients who applied to our hospital via 112 Emergency Health Services from centers outside the provincial borders of Bolu received IV t-PA treatment. After being evaluated by emergency physicians, these patients were directed to non-contrast CBT and MRI/DWI imaging. The on-call neurologist administered IV t-PA bolus and maintenance therapy at a standard dose (0.9 mg/kg) with the patients' consent.

3. Telestroke Group: Patients who received IV t-PA treatment via telestroke consultation from hospitals outside the borders of Bolu province and were transferred to our hospital emergency department. When these patients reached an external center where IV t-PA treatment could be applied within 4.5 hours of the onset of symptoms, they were evaluated by the emergency department and neurology physicians. The physicians at the external center transferred the patient's history and physical examination information to the on-call neurologist at our hospital by phone. The on-call neurologist remotely evaluated the neuroimaging performed at the external center and determined whether the patient was suitable for treatment. After the telestroke consultation, IV t-PA treatment was initiated by the external center physician upon the recommendation of the on-call neurologist and with the patient's consent. These patients were then transferred to our hospital stroke center for further neurovascular investigation and, if necessary, endovascular intervention.

All patient groups were followed for three months. Initial stroke severity was assessed with the NIHSS scale, and clinical outcomes were measured with mRS scores at the presentation and three months. mRS scores between 0 and 2 were defined as good, 3 and 4 as moderate, five as poor functional outcome, and six as mortality.

2.3. Statistical analysis: The normal distribution of the data was assessed using the Shapiro-Wilk test. To compare three or more groups, the Kruskal-Wallis test was utilized. The relationship between two categorical variables was analyzed using Pearson's chi-square test or Fisher's exact test. The single-sample chi-square test was applied for frequency analysis of a single

categorical variable. All analyses were conducted using SPSS version 23 (SPSS Inc., Armonk, NY). A significance level of $p < 0.05$ was established.

3. Results

In this study, we evaluated 198 patients diagnosed with acute ischemic stroke, highlighting the pressing need for timely intervention. The patients' ages ranged from 20 to 93 years, with an average age of 70.1 ± 13.3 years, revealing that a significant portion of those affected are older adults. Notably, 56.6% of participants were women (see Table 1), emphasizing the importance of gender considerations in stroke treatment. Our findings show that 74.24% of the patients were treated in the center group, 13.13% were in the telestroke group and 12.63% were transferred from other facilities. Alarmingly, the median time to reach the emergency department was 90 minutes (IQR: 60-120 minutes; minimum: 15 minutes, maximum: 280 minutes), highlighting potential delays in care that need to be addressed. Furthermore, regarding patient history, 10.1% had previously experienced a stroke, and 4.5% had undergone coronary artery bypass grafting. The median NIHSS score of 11 (IQR: 8-14; minimum: 1; maximum: 24) underscores the severity of neurological conditions in these patients (see Table 1) and reinforces the urgency of swift and efficient clinical responses.

When comparing the time from the onset of symptoms to a presentation at our emergency department among all patient groups, we found the following median arrival times: the telestroke group had a median of 87.5 minutes (IQR: 57.5-120), the transfer group had 90 minutes (IQR: 45-100), and the center group also had 90 minutes (IQR: 60-145). Statistical analysis showed no significant difference in arrival times to the emergency department among the telestroke, transfer, and center groups (χ^2=3.631, p=0.163). Next, we compared the durations from the

Table 1. General characteristics of the patients.

Parameter	**Mean ± SD / n**	**Med (IQR, Min-Max) / %**
Age, Year	70,1±13,3	72 (62-81, 20-93)
Gender		
Female	112	56,6
Male	86	43,4
Application location		
Center Group	147	74,2
Telestroke Group	26	13,1
Transfer Group	25	12,6
Arrival time, min	97±53,7	90 (60-120, 15-280)
History of stroke		
Absent	178	89,9
Present	20	10,1
History of bypass		
Absent	189	95,5
Present	9	4,5
Hypertension		
Absent	73	36,9
Present	125	63,1
Diabetes mellitus		
Absent	155	78,3
Present	43	21,7
Hyperlipidemia		
Absent	180	90,9
Present	18	9,1
Obesity		
Absent	194	98
Present	4	2
Coronary artery disease		
Absent	119	60,1
Present	79	39,9
NIHSS	11,3±4,8	11 (8-14, 1-24)
Etiology (TOAST classification)		
Large-artery atherosclerosis	52	26,3
Cardioembolism	34	17,2
Small-vessel occlusion (lacune)	52	26,3
Stroke of other determined etiology	60	30,3
Antiaggregant use		
Absent	126	63,6
Present	72	36,4
IV-tPA initiation time, min	126,4±59	120 (87,5-180, 25-310)

IQR: *Interquartile range,* ***NIHSS****: National Institutes of Health Stroke Scale,* ***TOAST:*** *Trial of Org 10172 in Acute Stroke Treatment.*

onset of symptoms to the start of IV-tPA treatment across all patient groups. The median duration for the center group was 120 minutes (IQR: 90-180), while for the telestroke group, it was 110 minutes (IQR: 67.5-157.5), and for the transfer group, it was 100 minutes (IQR: 60-120). We determined that patients in the center group had significantly longer recanalization times than those in the transfer group (χ^2=6.777, p=0.034, Post-Hoc: p=0.034).

Table 2. Clinical characteristics of patient groups.

Parameters	Total (n=198)	Center Group (n=147)	Telestroke Group (n=26)	Transfer Group (n=25)	*p*
Emergency department arrival time, min					
Mean±ss	97±53,7	99,4±51,7	101,9±72,6	77,8±37,9	
Med (Q1-Q3)	90 (60-120)	90 (60-145)	87,5 (57,5-120)	90 (45-100)	χ^2=3,631 0,163[a]
Min-Maks	15-280	15-210	30-280	15-180	
Time to receive IV-tPA time, min					
Mean±SD	126,4±59	130,6±56,2	128,8±80,5	98,8±41,1	
Med (Q1-Q3)	120 (87,5-180)	120 (90-180)	110 (67,5-157,5)	100 (60-120)	χ^2=6,777 0,034[a]
Min-Maks	25-310	25-240	40-310	30-210	
Admission mRS					
≤2	45	36 (24,5)	5 (19,2)	4 (16)	χ^2=1,133 0,889[b]
3-4	104	76 (51,7)	14 (53,8)	14 (56)	
5	49	35 (23,8)	7 (26,9)	7 (28)	
3. month mRS					
≤2	130	94 (63,9)	19 (73,1)	17 (68)	χ^2=3,863 0,335[c]
3-4	34	24 (16,3)	6 (23,1)	4 (16)	
5	34	29 (19,7)	1 (3,8)	4 (16)	

[a]: Kruskal Wallis, [b]: Pearson Chi-square, [c]: Fisher'ın Exact test.

The modified Rankin Scale (mRS) scores of the patients are presented in Table 2. Notably, no patient had a mRS score of 6. When examining the pre-treatment mRS scores, there was no significant difference among the groups (χ^2=1.133, p=0.889). Similarly, an analysis of the post-treatment mRS scores revealed no significant difference between the groups (p=0.335, χ^2=3.863, respectively) as shown in Table 2.

4. Discussion

In our study, the t-PA treatment durations and three-month mRS scores and mortality of patients who applied directly to our stroke center (center group), who were brought from an external center by 112 teams and received IV t-PA in our emergency department (transfer group), and who were treated with the drip and sent approach (telestroke group) were compared. No mortality was detected in the three groups in the three months. In our study, it was observed that the median time for patients in different groups to come to the emergency department

after stroke symptoms was 90 minutes (min: 15, max: 280), and the average time to receive IV-tPA was 120 minutes (min: 25, max: 310). When we looked at all three groups, no significant difference was found between the times to come to the emergency department. In the study by Murat et al., the mean time from the emergency department to recanalization was 89.63±48.29 minutes, and the mean time from symptom to recanalization was 137.32±52.44 minutes [17]. In the study by Kijpaisalratana et al., the time from the emergency department to recanalization and the time from symptom to recanalization were significantly longer in the group that came from an external center without IV t-PA (146.5±62 minutes) compared to direct admission (38±23 minutes) and in the group that came to the center after IV t-PA treatment (63±44 minutes) [18]. In the study by Gerschenfeld et al., the procedure times were longer in the group brought to the center after IV tPA was administered than in those brought to the center directly. The time from initial symptoms to arrival at the emergency department was 150 versus 135 minutes, while the time from onset to recanalization was 297 versus 240 minutes [19]. In the study conducted by Matsoukas et al., the time to IV t-PA was 87.5 minutes for those who received IV t-PA and were sent to the center, while it was 78.5 minutes for those who were brought directly to the stroke center [20]. Our study found no difference between the groups regarding the time to apply to the emergency department. When the groups were evaluated regarding the time to receive IV-tPA in our study, it was determined that treatment was started in the transfer group in a shorter time. We think that the reasons for these situations may be that the distance to the districts of Bolu province is greater than the distance to neighboring provinces due to the geographical characteristics, the winter season in Bolu province is long, the harsh weather causes delays in transportation, the elderly population mostly lives in rural areas, they do not understand the stroke symptoms or notice them late, and the delays in notifying their relatives and 112 teams may cause a delay in reaching the hospital. The National Institute of Neurological Disorders and Stroke study has shown that IV t-PA treatment has a consistent effect on the functional outcome of all ischemic stroke subtypes [21]. Our study observed a significant decrease in mRS scores (median value 2) measured 3 months after IV t-PA treatment compared to the initial mRS scores (median value 4). No significant difference was found between the mRS scores of the three patient groups we compared. In the study by Gerschenfeld et al., the rate of patients with a favorable neurologic outcome at 3 months was found to be similar in both groups: 61% in those who received IV t-PA treatment and were brought to the center and 50.8% in those who were brought directly to the emergency department [19]. In the study by Martin-Schild et al., no difference was found in the functional results of mRS scoring between the two patient groups, those brought directly to the center emergency department and those who received IV t-PA treatment from an external center [22]. In the study conducted by Park et al., the mean mRS scores after 3 months were compared between the groups and were found to be 44.4% for those who came directly to the central emergency department and 44.0% for those who received IV t-PA treatment and were brought to the center. As a result, no significant difference was found between the two groups [23]. In the study conducted by Matsoukas et al., 287 patients who underwent mechanical thrombectomy were included. The patients were classified as those who came directly to the central emergency department and those who received IV t-PA treatment and were brought to the center. No

statistically significant difference was shown for 3-month mortality in either group (20). The results of our study are similar to those of the literature. The 'drip and send method,' which is named for those who received IV t-PA treatment and were brought to the center to provide acute ischemic stroke treatment, increases the number of patients who can benefit from IV t-PA [24]. Patient selection for IV t-PA with the drip and send approach involves the relationship between the emergency department physician or neurologist, radiologist, and the neurologist at the stroke center. Our study found a significant decrease in mRS scores in the three groups we compared, similar to other studies, after 3 months. The use of drip-and-send IV t-PA for the treatment of acute ischemic stroke is likely to increase, and it is critically important to collect more safety data.

4.1. Limitations: This study has some limitations. First, the retrospective data collection may affect the results' reliability due to its retrospective nature. In addition, the limited sample size may make it difficult to detect slight differences and limit the results' generalizability. The fact that the study was conducted in a single center may limit the validity of the findings for different populations and regions. Considering these limitations, it should be kept in mind that the findings should be interpreted cautiously and that more significant scale, prospective studies are needed.

4.2. Conclusion*:* Reducing the time from non-stroke center hospitals to the emergency department is important to minimize the time to treatment in acute ischemic stroke. This could potentially improve long-term outcomes by providing faster treatment times for patients with acute ischemic stroke. There is a need to coordinate and improve the diagnosis and treatment of acute ischemic stroke. Further large-scale randomized prospective studies are needed to confirm these results.

Funding: *The authors received no financial support for the research, authorship, and/or publication of this article.*

Conflict of Interest: *The authors declared no conflict of interest.*

Ethical Statement: *Study procedures were performed in accordance with the Declaration of Helsinki. Our study was conducted with the permission of Bolu Abant İzzet Baysal University Ethics Committee dated 27/04/2021 and numbered 2021/95.*

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