Original Article

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# Comparison of Intracranial Hemorrhage and Clinical Outcomes Among Patients Undergoing Mechanical Thrombectomy with and without Thrombolytic Therapy

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## Abstract

**Aim:** It remains controversial whether intravenous tissue plasminogen activator (IV tPA) increases complications in patients undergoing mechanical thrombolysis. In this study, we aimed to show the effect of IV tPA administration on complications.

**Methods:** In this cross-sectional study, the records of patients who were followed up at the stroke center and underwent mechanical thrombectomy (MT) between 2022 and 2023 were retrospectively reviewed. Demographic data, cerebral angiography data, neuroimaging time, medical history, and medication use; neurologic examination findings at baseline, 24$^{th}$ hour, and 3$^{rd}$ month were obtained from the patient files. Patients were divided into two groups according to whether intracranial tPA was administered before MT and two groups according to the presence of intracranial hemorrhage at 24 hours.

**Results:** A total of 172 patients [94 women (54.7%) and 78 men (45.3%)] were included in the study. Mean age was 67.6±14.7 years. At 24 h, the rate of symptomatic intracranial hemorrhage (sICH) was significantly (p=0.004) higher in the thrombectomy group than in the tPA plus thrombectomy group. The admission (p=0.033) and 24-hour National Institutes of Health Stroke Scale (p=0.001) scores were significantly higher in the sICH group than in the non-sICH group. Third-month modified Rankin scale score (p=0.003), diastolic embolism rate (p=0.009), and Tan score (p=0.007) were significantly higher in the sICH group than in the non-sICH group.

**Conclusion:** Intravenous tissue plasminogen activator did not increase sICH or distal embolism in patients undergoing MT, and there was no difference in terms of favorable clinical outcomes. Symptomatic intracranial hemorrhage was associated with increased mortality and poor clinical outcome.

**Keywords:** Thrombectomy, thrombolytic therapy, intracranial hemorrhage

## Introduction

For acute ischemic stroke, clinicians use intravenous tissue plasminogen activator (IV tPA) alone or in combination with mechanical thrombectomy (MT). Intravenous tissue plasminogen activator has been shown to reduce the rate of disability in the first 3 hours after ischemic stroke (1). In 2008, IV tPA was shown to be effective for functional independence in patients with ischemic stroke who received IV tPA in the first 4.5 hours, but intracerebral bleeding rates were higher in these patients (2). Recent studies have shown that in addition to IV tPA, MT in large vessel occlusion reduces the rate of disability after ischemic stroke. Since IV tPA and MT were administered together in almost all of these studies, it remains a matter of debate whether IV tPA is beneficial for large vessel occlusions or whether it increases the complication rate. Some of the topics of these debates include whether it increases potential bleeding rates, whether it increases distal embolism by lysing the thrombus, or whether it increases door-puncture times. Along with these studies, the American Heart Association/American Stroke Association has recommended that patients with ischemic stroke receive IV tPA in the first 4.5 hours if there are no contraindications and MT if there is large vessel occlusion (3-7).

We hypothesized that administration of IV tPA before thrombectomy would not cause intracranial hemorrhage

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or distal embolism after the procedure. The present study aimed to investigate the effect of IV tPA administration on complications in patients undergoing mechanical thrombectomy.

## Materials and Methods

### Compliance with Ethical Standards

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (dated: 27.12.2023, approval no.: 260-2023) of the Declaration of Helsinki. Informed consent was obtained from all patients.

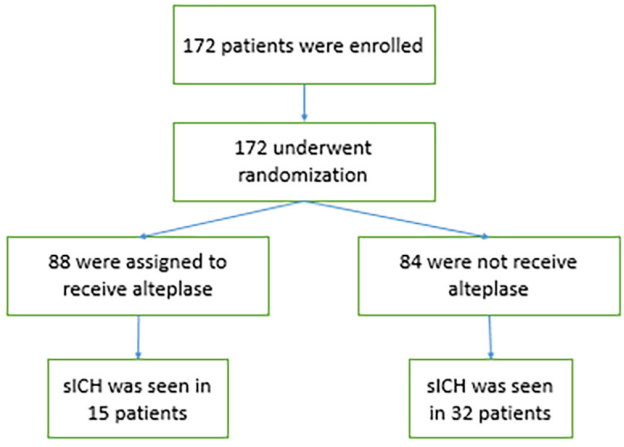
### Study Design

This study had a cross-sectional study design. The records of patients who underwent IV tPA and/or MT at stroke centers between 2022 and 2023 were retrospectively reviewed. Demographic data, angiography data, imaging times, medical history, medication use, and neurological examination findings at baseline, 24$^{th}$ hour, and 3$^{rd}$ month were obtained from the patient files. Patients were divided into 2 groups according to whether intracranial tPA was administered before MT and 2 groups according to the presence of intracranial hemorrhage at 24 hours (Graph 1).

### Patient Selection and Endovascular Treatment

Basilar artery, posterior cerebral artery P1 segment, internal carotid artery (ICA) (tandem, T, L) or middle cerebral artery (MCA) M1 segment occlusion, no bleeding on brain computed tomography (CT), Alberta Stroke Program Early CT (ASPECT) score >6, patients with a National Institutes of Health Stroke Scale (NIHSS) score of ≥6, a pre-stroke modified Rankin Scale (mRS) score of 0-1, a symptom-door time of less than 4.5 hours, a symptom-door time of 4.5-16 hours with diffusion weighted imaging/fluid-attenuated inversion recovery (FLAIR) discordance, and patients who underwent MT were included in the study. Table 1 presents the inclusion criteria.

Patients were evaluated by a neurologist at the emergency department presentation. All patients underwent noncontrast brain CT and CT angiography (CTA). Patients with no contraindications admitted in the first 4.5 hours after symptoms and those with no contraindications admitted for less than 16 hours with no ischemic lesion reflected on magnetic resonance imaging FLAIR sequence were started on alteplase at a dose of 0.9 mg/kg in the emergency department and then taken to the angio unit for MT. Mechanical thrombectomy was performed under conscious sedation or general anesthesia using a monoplane angiography device. The femoral artery was used as the access site for the procedure. A 6 French (F) guiding catheter (Destination, Terumo, Tokyo, Japan) was then placed in the subclavian artery, vertebral artery, common carotid artery, or cervical segment of the ICA. A distal access catheter (Catalyst 5F-6F Stryker, Kalamazoo, Michigan), a microcatheter (Rebar, Medtronic, Minneapolis, USA), and a 0.014-inch microwire (synchroo stryker) were used. Mechanical thrombectomy was performed using either stent retriever thrombectomy (isolated stent retriever, ARTS, SAVE, solumbra) or aspiration (ADAPT) techniques. The stent retriever was deployed in the occluded segment in the MT with the appropriate size (Trevo, Stryker, Kalamazoo, Michigan, USA; Thrombite, Zylox-Tonbridge, Hangzhou, China; Solitaire X, Medtronic, Minneapolis, USA). If the procedure failed after two attempts, the technique was changed. If the procedure was not successful despite seven thrombectomy procedures, the procedure was terminated. In tandem occlusions, direct aspiration was performed first, and if unsuccessful,




**Graph 1.** Numbers of patients
*sICH: Symptomatic intracranial hemorrhage*

**Table 1. Inclusion criteria**

| |
|---|
| 18-90 years old |
| Large vessel occlusion |
| Symptom-door time of less than 4.5 hours |
| Symptom-door time between 4.5 and 16 hours and no ischemic lesion reflected in the MRI image on the FLAIR sequence |
| NIHSS >6 |
| Pre-admission mRS 0-1 |
| ASPECT >6 |

MRI: Magnetic resonance imaging, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, ASPECT: Alberta Stroke Program Early Computed Tomography Score (CT-0 score), FLAIR: Fluid-attenuated inversion recovery

balloon angioplasty was performed at the internal carotid origin. In cases of reocclusion at the ICA origin despite balloon angioplasty, carotid artery stenting was performed after the administration of 300 mg of acetylsalicylic acid and 300 mg of clopidogrel.

We followed up patients who underwent MT in the intensive care unit after the procedure. We monitored the blood pressure and neurologic examination every 30 minutes for the first 2 hours, and then every hour thereafter. We performed a brain CT scan 24 hours after MT. The brain CT scan revealed no bleeding; we started antiaggregant or anticoagulant therapy to address the etiology.

### Clinical Evaluation Scales

Alberta Stroke Program Early CT scores were rated on cranial CT (8). Modified Tan scoring was used to obtain a collateral score on the CTA (9). The recanalization level was evaluated according to the modified treatment in cerebral ischemia (mTICI) classification. Accordingly, mTICI 0 was defined as no flow, mTICI 1 as filling of the distal MCA but no blood supply to the cortical branches, mTICI 2a as less than half of the MCA irrigation area, mTICI 2b as more than half of the MCA irrigation area, mTICI 2c as the entire MCA irrigation area but more slowly than the normal side, and mTICI 3 as complete recanalization. After the first thrombectomy attempt, mTICI 2c-3 recanalization was considered first-pass recanalization (10). Bleeding causing an increase of ≥4 points according to admission NIHSS score was defined as symptomatic ICH. Disability status on day 90 was evaluated with mRS.

### Statistical Analysis

SPSS 28.0 software was used for the analyses. Mean, standard deviation, median minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by Kolmogorov-Smirnov. Kruskal-Wallis, Mann-Whitney U tests were used to analyze quantitative, independent data. The chi-square test was used in the analysis of qualitative independent data, and the Fisher's exact test was used when chi-square test conditions were not met. The results were evaluated at a significance level of $p<0.05$.

## Results

A total of 172 patients [94 women (54.7%) and 78 men (45.3%)] who met the inclusion criteria (Table 1) between 2022 and 2023 were included in the study. The mean age was 67.6±14.7 years, the mean ASPECT at presentation was 9.1±1.1, and history of previous stroke was 33 patients (19.2%). IV tPA was administered in 88 (51.2%) patients. The mean symptom-puncture time was 250.6±174.3 minutes, symptom-canalization time was 308.3±181.2 minutes, puncture-canalization time was 56.8±24.0 minutes, door-imaging time was 19±15.8 minutes, door-IV tPA time was 51.2±20.9 minutes, and door-puncture time was 56.5±17.5 minutes. The successful recanalization rate (TICI 2B, 2C, 3) was 86.1%. At 24 hours, intracranial hemorrhage was seen in 47 (27.3%) patients (Table 2).

**Table 2. General information about patients undergoing thrombectomy**

| | | Min.-Max. | Mean ± SD/n% |
|---|---|---|---|
| Age | | 21.0-90.0 | 67.6±14.7 |
| Sex | Woman | | 94/54.7% |
| | Man | | 78/45.3% |
| Cigarette smoking | (-) | | 99/57.6% |
| | (+) | | 73/42.4% |
| **Comorbid disease** | | | |
| Hypertension | | | 100/58.1% |
| Atrial fibrillation | | | 72/41.9% |
| Coronary artery disease | | | 71/41.3% |
| Diabetes mellitus | | | 48/27.9% |
| Obesity | | | 44/25.6% |
| Stroke history | (-) | | 139/80.8% |
| | (+) | | 33/19.2% |
| Admission aspect | | 5.0-10.0 | 9.1±1.1 |
| Warfarin use | (-) | | 162/94.2% |
| | (+) | | 10/5.8% |

| Table 2. Continued | | | |
|---|---|---|---|
| | | **Min.-Max.** | **Mean ± SD/n%** |
| NOAC use | (-) | | 153/89.0% |
| | (+) | | 19/11.0% |
| IV tPA | (-) | | 84/48.8% |
| | (+) | | 88/51.2% |
| Symptom puncture time | | 15.0-795.0 | 250.6±174.3 |
| Symptom recanalisation time | | 75.0-815.0 | 308.3±181.2 |
| Puncture recanalization time | | 10.0-190.0 | 56.8±24.0 |
| The door imaging time | | 2.0-120.0 | 19.0±15.8 |
| Door tPA time | | 20.0-120.0 | 51.2±20.9 |
| Door puncture time | | 15.0-110.0 | 56.5±17.5 |
| **NIHSS score** | | | |
| Admission | | 3.0-22.0 | 9.7±3.5 |
| $24_{th}$ hour | | 0.0-25.0 | 6.2±4.9 |
| $3_{rd}$ month mRS score | | 0.0-6.0 | 2.4±2.0 |
| Glucose | | 76.0-608.0 | 148.8±75.7 |
| sICH in 24 hours | | (-) | 125/72.7% |
| (+) | | 47/27.3% | |

SD: Standard deviation, ASPECT: Alberta Stroke Program Early Computed Tomography Score (CT-0 score), NOAC: new oral anticoagulant, IV tPA: Intravenous tissue plasminogen activator, mRS: Modified rankin scale, NIHSS: National institutes of health stroke scale, sICH: Symptomatic intracranial hemorrhage

Symptom puncture (p=0.000), symptom recanalization (p=0.000), and puncture recanalization (p=0.021) time were significantly higher in the thrombectomy group than in the tPA plus thrombectomy group. In our study, the use of stent retrievers did not differ significantly between the IV tPA plus thrombectomy and thrombectomy groups. The rate of symptomatic intracranial hemorrhage (sICH) in the thrombectomy group at admission 24 hours was significantly (p=0.004) higher than that in the tPA plus thrombectomy group, and there was no superiority between the two groups in the 3rd month mRS scores ($0.971^{m}$) (Table 3).

The smoking rate was significantly lower (p=0.045) in the group with sICH than in the group without sICH. History of stroke was significantly (p=0.039) higher in the group with sICH than in the group without sICH. The IV door-IV tPA rate was significantly (p=0.004) lower in the sICH group than in the non-sICH group. Admission (p=0.033), 24th hour (p=0.001) the NIHSS score was significantly (p<0.05) higher in the group with sICH than in the group without sICH. The 3rd month mRS score was significantly (p=0.003) higher in the sICH group than in the non-sICH group. The distal embolism rate was significantly (p=0.009) higher in the sICH group than in the non-sICH group. The Tan score was significantly (p=0.007) lower in the sICH group than in the non-sICH group (Table 4).

## Discussion

In this study, the effects of intravenous tissue plasminogen activator (IV tPA) administration on mechanical thrombectomy (MT) time, complications during the MT procedure, and intracerebral hemorrhage (ICH) in patients undergoing MT were analyzed. In a single-center retrospective study of 250 patients (105 with IV tPA plus MT and 145 with MT alone), symptom and door puncture times were found to be shorter in the MT group (11). It was found that IV tPA administration did not affect the thrombectomy door-puncture time; on the contrary, the puncture recanalization time was longer in the thrombectomy-only group than in the thrombectomy plus IV tPA group (p<0.05). In our study, first-pass recanalization, use of a stent retriever, and distal embolism rates did not differ significantly (p>0.05) between the IV tPA plus thrombectomy and thrombectomy groups. Therefore, administration of IV tPA may not be a disadvantage in terms of the initiation of MT therapy or development of procedural complications.

Several recent studies have evaluated the efficacy of MT in patients with acute stroke by comparing it with combined IV tPA plus MT therapy (11-14). A meta-analysis showed that combined IV tPA plus MT was associated with a higher probability of functional independence than MT alone. However, these results were derived from retrospective cohort studies in which MT alone was

| Table 3. Comparison between thrombectomy and combined tPA plus thrombectomy | | | | |
|---|---|---|---|---|
| Mean ± SD/n% | | tPA plus thrombusectomy<br>Mean ± SD/n% | Thrombectomy | p-value |
| Age | | 66.8±15.5 | 68.5±13.8 | 0.484[m] |
| Sex | Woman | 49/55.7% | 45/53.6% | 0.781[X²] |
| | Man | 39/44.3% | 39/46.4% | |
| Cigarette smoking | (-) | 49/55.7% | 50/59.5% | 0.610[X²] |
| | (+) | 39/44.3% | 34/40.5% | |
| **Comorbid disease** | | | | |
| Hypertension | | 47/53.4% | 53/63.1% | 0.198[X²] |
| Atrial fibrillation | | 34/38.6% | 38/45.2% | 0.380[X²] |
| Coronary artery disease | | 39/44.3% | 32/38.1% | 0.407[X²] |
| Diabetes mellitus | | 25/28.4% | 23/27.4% | 0.881[X²] |
| Obesity | | 22/25.0% | 22/26.2% | 0.858[X²] |
| Stroke history | (-) | 72/81.8% | 67/79.8% | 0.732[X²] |
| | (+) | 16/18.2% | 17/20.2% | |
| Admission aspect | | 9.3±1.1 | 9.0±1.1 | 0.127[m] |
| Symptom puncture time | | 156.4±96.3 | 311.1±186.4 | **0.000**[m] |
| Symptom recanalisation time | | 207.1±97.6 | 373.3±192.7 | **0.000**[m] |
| Puncture recanalization time | | 51.2±19.5 | 60.4±26.0 | **0.021**[m] |
| The door imaging time | | 16.4±10.0 | 21.7±19.8 | 0.117[m] |
| Door tPA time | | 51.7±21.1 | 36.7±5.8 | 0.177[m] |
| Door puncture time | | 58.9±17.2 | 54.9±17.6 | 0.233[m] |
| **NIHSS score** | | | | |
| Admission | | 9.1±3.1 | 10.3±3.8 | **0.032**[m] |
| 24th hour | | 5.8±4.7 | 6.6±5.0 | 0.246[m] |
| 3rd month mRS score | | 2.40±2.06 | 2.32±1.96 | 0.971[m] |

[m]Mann-Whitney U test, [X²]Chi-square test
Bold values: p<0.05
SD: Standard deviation, ASPECT: Alberta Stroke Program Early Computed Tomography Score (CT-0 score), NOAC: new oral anticoagulant, IV tPA: Intravenous tissue plasminogen activator, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale

| Table 4. Comparison of patients with and without hemorrhage | | | | |
|---|---|---|---|---|
| | | sICH (-)<br>Mean ± SD/n% | sICH (+)<br>Mean ± SD/n% | p-value |
| Age | | 67.7±14.6 | 68.0±15.0 | 0.847[m] |
| Sex | Woman | 63/50.4% | 31/65.9% | 0.094[X²] |
| | Man | 62/49.6% | 16/34.1% | |
| Cigarette smoking | (-) | 66/52.8% | 33/70.2% | **0.045**[X²] |
| | (+) | 59/47.2% | 14/29.8% | |
| Hypertension | | 77/61.6% | 23/48.9% | 0.155[X²] |
| Atrial fibrillation | | 51/40.8% | 21/44.6% | 0.569[X²] |
| Coronary artery disease | | 57/45.6% | 14/29.7% | 0.068[X²] |
| Diabetes mellitus | | 36/20.8% | 12/25.5% | 0.574[X²] |
| Obesity | | 33/26.4% | 11/23.4% | 0.516[X²] |
| Stroke history | (-) | 106/84.8% | 33/71.7% | **0.039**[X²] |
| | (+) | 19/15.2% | 14/28.3% | |

| Table 4. Continued | | | | | |
|---|---|---|---|---|---|
| | | | sICH (-) | sICH (+) | p-value |
| | | | Mean ± SD/n% | Mean ± SD/n% | |
| Admission aspect | | | 9.2±1.0 | 8.9±1.3 | 0.134[m] |
| Warfarin use | (-) | | 119/95.2% | 43/91.3% | 0.842[X²] |
| | (+) | | 6/4.8% | 4/8.7% | |
| NOAC use | (-) | | 113/91.1% | 38/82.6% | 0.117[X²] |
| | (+) | | 11/8.9% | 8/17.4% | |
| IV tPA | (-) | | 52/42.4% | 32/68.1% | **0.004**[X²] |
| | (+) | | 73/57.6% | 15/32.9% | |
| Symptom puncture time | | | 248.1±176.3 | 256.3±171.5 | 0.609[m] |
| Symptom recanalisation time | | | 306.0±183.0 | 313.6±178.9 | 0.644[m] |
| Puncture recanalization time | | | 57.6±24.3 | 54.9±23.7 | 0.398[m] |
| The door imaging time | | | 17.6±13.5 | 22.9±20.5 | 0.127[m] |
| Door tPA time | | | 50.4±19.3 | 53.8±28.3 | 0.961[m] |
| Door puncture time | | | 56.3±18.0 | 57.1±16.4 | 0.877[m] |
| **NIHSS score** | | | | | |
| Admission | | | 9.3±3.3 | 10.8±4.0 | **0.033**[m] |
| 24th hour | | | 5.4±4.6 | 8.3±5.2 | **0.001**[m] |
| 3rd month mRS score | | | 2.11±1.96 | 3.04±2.03 | **0.003**[m] |
| Glucose | | | 146.3±72.6 | 149.2±72.8 | 0.610[m] |
| HB | | | 12.5±2.3 | 12.1±2.2 | 0.339[m] |
| PLT | | | 250.5±113.0 | 244.0±79.4 | 0.798[m] |
| Stent retriever usage (+) | | (-) | 29/29.9% | 10/24.4% | 0.511[X²] |
| | | 68/70.1% | 31/75.6% | | |
| Distal embolism (+) | | (-) | 59/60.8% | 15/36.6% | **0.009**[X²] |
| | | 38/39.2% | 26/63.4% | | |
| Antiaggregant therapy (+) | | (-) | 70/56.0% | 27/57.4% | 0.993[X²] |
| | | 55/44.0% | 20/42.6% | | |
| Tan score<br><50%<br>50-99%<br>100% | | (-) | 17/19.1% | 18/45.0% | **0.007** [X²] |
| | | 25/28.1% | 6/15.0% | | |
| | | 31/34.8% | 14/35.0% | | |
| | | 16/18.0% | 2/5.0% | | |

[m]Mann-Whitney U test, [X²]Chi-square test
Bold values: p<0.05
SD: Standard deviation, ASPECT: Alberta Stroke Program Early Computed Tomography Score (CT-0 score), NOAC: new oral anticoagulant, IV tPA: Intravenous tissue plasminogen activator, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, sICH: Symptomatic intracranial hemorrhage

administered to many patients who were not eligible for IV tPA (15). Kaesmacher et al. (16) showed that MT alone was not superior to combined IVT-MT in terms of good clinical outcomes in a meta-analysis of patients admitted only during the IV tPA window. In our study, no superiority was found between the two groups in 3rd month mRS scores (p<0.05).

ICH is associated with high morbidity and mortality after MT (17). It is known that IV tPA administration alone increases the rate of ICH 3 to 10-fold compared to placebo (18,19). Yang et al. (20) showed that the symptomatic ICH rates were similar between patients treated with MT alone and combined therapy. The DEVT study revealed a higher incidence of ICH in patients receiving IV tPA (21). In a prospectively designed study, Quang Anh et al. (22) reported that combined treatment did not increase the risk of ICH. A 2021 meta-analysis found that combination therapy did not increase the risk of ICH (23). This study showed that the occurrence of ICH within 24 hours of symptom onset was significantly reduced in the combined group compared with the MT alone group (p<0.05). This may be explained by the fact

that the MT group's symptom-puncture and symptom recanalization times were higher than those of the tPA plus MT group ($p<0.05$). In our study, we also compared patients with and without ICH at 24 hours. In the group with ICH, admission and 24-hour NIHSS score were significantly ($p<0.05$) higher than the group without ICH. The 3rd month mRS score was significantly ($p<0.05$) higher in the ICH group than in the non-ICH group. These findings showed that ICH increased mortality and decreased functional independence, consistent with the literature. Further studies are needed to clarify the relationship between the incidence of ICH, factors causing ICH, and patient outcomes.

In support of the view that the technique used during the MT procedure causes variability in the risk of ICH, the use of a stent retriever has been shown to cause more damage to the vessel wall, especially the endothelium, than the direct aspiration technique (24). Contrary to this argument, Yıldırım (25) showed that the ICH rates were similar between the two techniques. In our study, no difference was observed in the rates of stent retrievers in patients with and without ICH. In our study, the rate of distal embolism was significantly ($p<0.05$) higher in the group with bleeding than in the group without bleeding. The fact that distal embolism is known to increase the volume of necrosis and cerebral edema and to increase the risk of hemorrhage is consistent with our study results.

### Study Limitations

Our study's first limitation was that it was retrospective in nature. Another limitation was that the number of participants in the sample group was small due to the first year of activity at the stroke center. Different results can be obtained with larger study groups. All patients did not receive full-dose IV tPA. Patients who underwent TICI 3 recanalization during the MT procedure had their iv tPA treatment discontinued before completion. The IV tPA doses were not evaluated in these patients. Despite these limitations, 250 patients were included in our study, and their neuroimaging findings were examined in detail. We believe that the patient outcomes in our stroke center, which works intensively and is in close communication with other departments, will make an important contribution to the literature.

## Conclusion

In patients undergoing MT, IV tPA administration did not increase ICH, or distal embolism, and there was no difference in terms of good clinical outcomes. ICH was found to be associated with increased mortality and poor clinical outcome. Further studies with larger patient groups are needed on this subject.

### Footnote

**Ethics Committee Approval:** Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (dated: 27.12.2023, approval no.: 260-2023).

**Informed Consent:** Informed consent was obtained from all patients.

**Authorship Contributions**

Surgical and Medical Practies: Z.M., Concept: Z.M., I.K., Design: Z.M., I.K., Data Collection or Processing: Z.M., I.K., Analysis or Interpretation: Z.M., I.K., Literature Search: Z.M., I.K., Writing: Z.M., I.K.

**Conflict of Interest:** No conflicts of interest were declared by the authors.

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