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Research Article

Comparative Study of Outcomes in Stroke Patients Receiving TPA within 3 vs. 4.5 Hours of Symptom Onset

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ABSTRACT
Background: Timely administration of tissue plasminogen activator (tPA) is crucial for effective stroke management, but the optimal therapeutic window remains under debate. This study examines the outcomes of stroke patients treated with tPA within two distinct time frames: within 3 hours and between 3 to 4.5 hours of symptom onset. **Methods:** In this retrospective cohort study, 180 stroke patients (90 in each group) treated at a tertiary care center were analyzed. Patients receiving tPA within 3 hours of onset were compared with those treated within 4.5 hours regarding functional outcomes, complication rates, and long-term disability and mortality. Functional independence, neurological improvement, and incidence of complications such as intracerebral hemorrhage were assessed. Statistical significance was determined using chi-square and t-tests, with a p-value <0.05 considered significant. **Results:** Patients treated within 3 hours showed a higher rate of functional independence at 3 months (54% vs. 47%, p=0.29) and better improvement in NIHSS scores. The incidence of intracerebral hemorrhage was lower in the 3-hour group (6.7% vs. 13.3%, p=0.05). Moreover, earlier treatment was associated with lower rates of severe disability and mortality at 6 months, although these differences did not reach statistical significance. **Conclusion:** This study suggests that treating stroke patients with tPA within 3 hours of symptom onset may lead to better functional outcomes and fewer complications compared to treatment within 4.5 hours. Despite the non-significant differences in some outcomes, the findings support the current clinical emphasis on the earliest possible administration of tPA.

Keywords: Stroke management, tissue plasminogen activator, therapeutic window

INTRODUCTION

Stroke represents one of the most devastating global health challenges, ranking as a leading cause of disability and the second leading cause of death worldwide. The introduction of tissue plasminogen activator (tPA) as a treatment for acute ischemic stroke marked a significant milestone in therapeutic interventions, offering the potential to reduce the burden of disability by restoring blood flow to the brain. However, the effectiveness of tPA is highly contingent on the timing of its administration post-symptom onset.[1]

The time window for optimal tPA administration has been a subject of extensive research and debate. Current guidelines primarily recommend administration within a 3-hour window, yet emerging data suggest extending this to 4.5 hours could benefit a broader spectrum of patients while maintaining safety and efficacy. This study seeks to delve into the comparative outcomes of stroke patients receiving tPA within these time frames, focusing on clinical efficacy and safety outcomes[2].

This comparative analysis is pivotal for several reasons. First, extending the therapeutic window

could significantly increase the number of patients eligible for tPA treatment. Second, understanding the differential outcomes within these time frames can aid in refining treatment protocols and emergency response strategies. Lastly, such a study can provide insights into the pathophysiological nuances of stroke progression and tPA intervention efficacy over time.[3]

Numerous studies have highlighted the benefits and risks associated with tPA administration. While the benefits of early treatment with tPA within three hours are well-documented, including reduced mortality and improved functional outcomes, the extension to 4.5 hours is supported by varying degrees of evidence suggesting a modest but significant benefit in select patient populations. The efficacy and safety beyond three hours remain contentious, with concerns about increased risks of intracerebral hemorrhage and other complications [4].

Aim

To compare the outcomes of stroke patients treated with tPA within 3 versus 4.5 hours of symptom onset.

Objectives

1. To evaluate the functional outcomes of stroke patients receiving tPA within 3 hours versus those treated within 4.5 hours.
2. To assess the incidence of intracerebral hemorrhage and other complications associated with tPA administration in these time frames.
3. To analyze the impact of treatment timing on long-term disability and mortality rates.

MATERIAL AND METHODOLOGY

Source of Data

The study utilized patient data retrospectively collected from the stroke registry at a large tertiary care center.

Study Design

This was a retrospective cohort study comparing two groups of stroke patients based on the timing of tPA administration.

Study Location

The study was conducted at tertiary care hospital.

Study Duration

Data were collected from January 2022 to December 2024.

Sample Size

A total of 180 patients were included in the study, with 90 patients in each group based on the tPA administration timing.

Inclusion Criteria

Patients aged 18 and older, diagnosed with ischemic stroke, who received tPA treatment within 4.5 hours of symptom onset were included.

Exclusion Criteria

Patients with hemorrhagic stroke, those who received tPA beyond 4.5 hours, or had contraindications to tPA therapy such as recent surgery, were excluded.

Procedure and Methodology

Patients were retrospectively assigned to two groups based on the tPA administration timing: within 3 hours and between 3 to 4.5 hours post-symptom onset. Clinical data were extracted including demographic information, stroke severity at presentation, time to tPA administration, and outcomes.

Sample Processing

Patient data were anonymized and standardized to ensure uniformity and confidentiality before analysis.

Statistical Methods

Data were analyzed using SPSS software. Chi-square and t-tests were used for categorical and continuous variables, respectively. Multivariate logistic regression was employed to adjust for potential confounders.

Data Collection

Data were collected from electronic health records, including demographics, clinical history, timing of tPA administration, and follow-up data on clinical outcomes and complication

OBSERVATION AND RESULTS

Table 1: Overall Outcomes of Stroke Patients Treated with TPA

Outcome	3 Hours Group	4.5 Hours Group	Test of Significance	95% CI	P-value

	(n=90)	(n=90)			
Mean Age (years)	68.4 (±11.2)	70.1 (±10.8)	t-test	(66.9, 69.9) - (68.7, 71.5)	0.26
Gender (Male)	54 (60%)	48 (53%)	χ^2-test	-	0.34
NIHSS Score at Admission	14.2 (±4.6)	15.3 (±4.3)	t-test	(13.5, 14.9) - (14.7, 15.9)	0.18
Time to Treatment (minutes)	155.4 (±20.1)	205.8 (±18.9)	t-test	(153.2, 157.6) - (203.9, 207.7)	<0.001
Functional Independence at 3 mo.	49 (54%)	42 (47%)	χ^2-test	-	0.29

Table 1 presents a comparative analysis of stroke patients treated with tPA within 3 hours and those treated within 4.5 hours. The mean age of participants was slightly higher in the 4.5 hours group (70.1 years) compared to the 3 hours group (68.4 years), although this difference was not statistically significant (p=0.26). Gender distribution showed a higher percentage of males in the 3 hours group (60%) versus the 4.5 hours group (53%), but again, the difference was not significant (p=0.34). The NIHSS score at admission indicated slightly more severe strokes in the 4.5 hours group (15.3) compared to the 3 hours group (14.2), but this was not statistically significant (p=0.18). However, the time to treatment significantly differed, with the 3 hours group treated more promptly (155.4 minutes) compared to the 4.5 hours group (205.8 minutes), with a p-value of less than 0.001. Functional independence at 3 months was observed more frequently in the 3 hours group (54%) than in the 4.5 hours group (47%), although this difference was not statistically significant (p=0.29).

Table 2: Functional Outcomes of Stroke Patients

Outcome	3 Hours Group (n=90)	4.5 Hours Group (n=90)	Test of Significance	95% CI	P-value
Modified Rankin Scale 0-2	56 (62%)	49 (54%)	χ^2-test	-	0.21
Barthel Index (Mean, SD)	85.3 (±15.2)	79.6 (±16.4)	t-test	(83.1, 87.5) - (77.2, 82.0)	0.04
NIHSS Improvement ≥4 points	72 (80%)	65 (72%)	χ^2-test	-	0.18

This table examines the functional outcomes post-tPA administration. The proportion of patients achieving a Modified Rankin Scale score of 0-2 was higher in the 3 hours group (62%) compared to the 4.5 hours group (54%), though this did not reach statistical significance (p=0.21). However, the Barthel Index, which measures daily living abilities, was significantly higher in the 3 hours group (85.3) than in the 4.5 hours group (79.6), with a p-value of 0.04, indicating a meaningful difference in recovery between the groups. Improvement of 4 or more points on the NIHSS was also more common in the 3 hours group (80%) compared to the 4.5 hours group (72%), but this was not statistically significant (p=0.18).

Table 3: Incidence of Complications

Complication	3 Hours Group (n=90)	4.5 Hours Group (n=90)	Test of Significance	P-value
Intracerebral Hemorrhage	6 (6.7%)	12 (13.3%)	χ^2-test	0.05
Symptomatic Hemorrhage	3 (3.3%)	7 (7.8%)	χ^2-test	0.19
Major Systemic Complications	8 (8.9%)	11 (12.2%)	χ^2-test	0.34

Complications following tPA treatment are summarized in Table 3. Intracerebral hemorrhage was notably less frequent in the 3 hours group (6.7%) compared to the 4.5 hours group (13.3%), with a p-value approaching significance (0.05), suggesting a potential trend toward higher risk with later treatment. Symptomatic hemorrhage and major systemic complications were also slightly more common in the 4.5 hours group, but these differences were not statistically significant (p=0.19 and p=0.34, respectively).

Table 4: Impact of Treatment Timing on Long-term Disability and Mortality Rates

Outcome	3 Hours Group (n=90)	4.5 Hours Group (n=90)	Test of Significance	P-value
Mortality at 6 Months	7 (7.8%)	12 (13.3%)	χ^2-test	0.12
Severe Disability (mRS 4-5)	13 (14.4%)	18 (20%)	χ^2-test	0.25
Post-Stroke Depression	18 (20%)	22 (24.4%)	χ^2-test	0.42

Table 4 focuses on long-term outcomes. Mortality at 6 months was higher in the 4.5 hours group (13.3%) compared to the 3 hours group (7.8%), but this was not statistically significant (p=0.12). Similarly, severe disability rates were higher in the 4.5 hours group (20%) versus the 3 hours group (14.4%), again without reaching statistical significance (p=0.25). Post-stroke depression was more prevalent in the 4.5 hours group (24.4%) than in the 3 hours group (20%), but this difference was not significant (p=0.42).

DISCUSSION

Table 1: Overall Outcomes of Stroke Patients Treated with tPA Table 1 outlines the basic demographics and initial response to treatment in two groups of stroke patients treated with tPA within different time windows: within 3 hours and within 4.5 hours of symptom onset. The mean age was slightly higher in the 4.5 hours group (70.1 years) compared to the 3 hours group (68.4 years), although the difference was not statistically significant (p=0.26). Le SM et al.(2020)[5] The distribution of males also showed no significant difference between the two groups. Notably, the time to treatment was significantly longer in the 4.5 hours group, with an average of 205.8 minutes compared to 155.4 minutes in the 3 hours group, reflecting the critical time-sensitivity of stroke treatment (p<0.001). The NIHSS scores at admission, which indicate the severity of stroke, were slightly worse in the 4.5 hours group, though not significantly (p=0.18). Functional independence at 3 months showed a higher percentage in the 3 hours group (54%) versus the 4.5 hours group (47%), but this difference did not reach statistical significance (p=0.29). Hassan AE et al.(2021)[6]

Table 2: Functional Outcomes of Stroke Patients This table delves into the functional outcomes measured by the Modified Rankin Scale, Barthel Index, and NIHSS improvement. A higher percentage of the 3 hours group achieved a Modified Rankin Scale score of 0-2, indicating better functional outcomes (62% vs. 54%), though this was not statistically significant (p=0.21). However, the Barthel Index, which measures daily living abilities, was significantly higher in the 3 hours group (85.3 vs. 79.6, p=0.04), suggesting better recovery in activities of daily living for those treated earlier. Improvement in NIHSS of 4 or more points was more common in the 3 hours group (80% vs. 72%), highlighting better neurological recovery, though this difference was not statistically significant (p=0.18). Messé SR et al.(2016)[7] & Soeteman DI et al.(2017)[8]

Table 3: Incidence of Complications This table compares the incidence of complications such as intracerebral hemorrhage, symptomatic hemorrhage, and major systemic complications between the groups. The incidence of intracerebral hemorrhage was notably higher in the 4.5 hours group (13.3% vs. 6.7%), with the p-value nearing significance (p=0.05), indicating a potential increased risk with later treatment. Rates of symptomatic hemorrhage and major systemic complications were also higher in the 4.5 hours group but did not reach statistical

significance. Al Kasab S et al.(2018)[9] & Brandel MG et al.(2020)[10]

Table 4: Impact of Treatment Timing on Long-term Disability and Mortality Rates Long-term outcomes such as mortality, severe disability, and post-stroke depression were analyzed in this table. Mortality at 6 months was higher in the 4.5 hours group (13.3% vs. 7.8%), though this was not statistically significant (p=0.12). The same trend was observed with severe disability (mRS 4-5) and post-stroke depression, both more frequent in the 4.5 hours group, indicating worse long-term outcomes with later treatment timing, yet these differences did not achieve statistical significance. Brandel MG et al.(2020)[11] & Tsivgoulis G et al.(2020)[12]

CONCLUSION

This comparative study aimed to analyze the differences in outcomes between stroke patients receiving tissue plasminogen activator (tPA) within 3 hours and those treated within 4.5 hours of symptom onset. The findings suggest that the timing of tPA administration plays a crucial role in determining the efficacy and safety of stroke treatment.

Patients who received tPA within the earlier 3-hour window generally demonstrated better functional outcomes, as evidenced by higher scores on the Modified Rankin Scale and Barthel Index, indicating greater functional independence and better daily living capabilities. Notably, these patients also exhibited a lower incidence of severe complications such as intracerebral hemorrhage, which was less common in the 3-hour group compared to those treated within 4.5 hours.

Furthermore, the study highlighted a trend towards reduced long-term disability and mortality in patients treated sooner. Although not all findings reached statistical significance, the patterns observed emphasize the potential benefits of earlier intervention. The significant difference in time to treatment between the groups underlines the importance of rapid medical response and stroke symptom recognition.

In conclusion, this study reinforces the current guidelines that advocate for the administration of tPA at the earliest possible within the therapeutic window. Extending treatment beyond 3 hours up to 4.5 hours remains a viable option for some patients; however, it is associated with slightly higher risks and somewhat diminished benefits. These findings underscore the necessity for ongoing education and improvement in stroke response systems to ensure that patients receive the most effective care promptly.

Limitations of Study

1. **Retrospective Design**: Being a retrospective analysis, this study is inherently limited by the quality and completeness of recorded data. Such designs are also more susceptible to biases in data collection and interpretation compared to prospective trials.
2. **Sample Size**: Although the total sample size was adequate to detect differences between the two groups, the study might still be underpowered for detecting smaller but clinically meaningful differences, especially in the sub-analyses of complications and long-term outcomes.
3. **Generalizability**: The study was conducted at a single center, which may limit the generalizability of the findings to other settings or populations. Different stroke management protocols, patient demographics, or healthcare systems could yield different results.
4. **Timing of Assessment**: The outcomes were assessed at three months post-stroke, which might not capture late recoveries or complications. Longer follow-up periods could provide a more comprehensive view of the prognosis and ongoing recovery patterns.
5. **Selection Bias**: As the assignment to treatment timing was not randomized, there may be inherent biases affecting which patients received treatment sooner. Factors influencing early or late treatment, such as stroke severity, initial misdiagnosis, or transport delays, could also influence outcomes independently of tPA administration.
6. **Confounding Variables**: There are potential confounding variables not fully controlled for in the analysis, such as variations in stroke subtype, the exact location of the clot, comorbid conditions, and previous use of anticoagulants or

antiplatelets, which could affect both the likelihood of receiving tPA and the outcomes following its administration.

7. **Statistical Limitations**: The statistical methods, while robust, are reliant on the assumption that the data are accurately recorded and normally distributed. The study also did not adjust for multiple comparisons in the analysis of various outcomes, which might increase the risk of type I errors.
8. **Missing Data**: The presence of missing data in some of the key variables could have introduced bias in the results if the missingness was not completely random.

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