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Thrombolysis Treatment in Patients Who Are Awake and Have an Unknown Duration of Stroke Receiving Effective and Safe Treatment or Who Are Futile and At Risk: A Study-Based SITS

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ABSTRACT

Background & Objective: Stroke is a leading cause of death worldwide, with approximately 800,000 new cases and 140,000 deaths annually in the United States. Intravenous tissue plasminogen activator (IV tPA) is the standard treatment for acute ischemic stroke (AIS) within a 4.5-hour window. Wake-up stroke (WUS), where the exact onset time is unknown, poses challenges for tPA treatment because of its uncertain timing. This study evaluated the efficacy and safety of IV tPA in WUS patients, with a focus on clinical outcomes and adverse effects.

Materials & Methods: This single-center, open-label clinical trial was conducted at the Vali-e-Asr Hospital Stroke Care Unit, Zanjan, Iran. A total of 107 patients with WUS were enrolled and divided into two groups: 53 who received IV tPA and 54 who did not receive thrombolysis. The inclusion criteria included acute neurological symptoms consistent with stroke upon waking and presentation within four hours of symptom onset. The exclusion criteria included various factors, such as intracranial hemorrhage, contraindications to MRI, severe comorbidities, and recent use of anticoagulants. Patient evaluations included NIHSS scores at admission and also at discharge, mRS scores at discharge and three months after stroke, and imaging with MRI and CT. Descriptive statistics, nonparametric tests, and regression analyses were used for data analysis.

Results: The tPA group had significantly lower discharge NIHSS scores (4.51 vs. 6.98, p=0.006) and lower in-hospital mortality rates (3.8% vs. 22.2%, p=0.008). At three months, the tPA group had a greater proportion of favorable mRS scores (mRS 0–1: 60.4% vs. 11.1%, p<0.001) and lower total mortality (6 vs. 17 deaths, p=0.011). No significant differences in adverse effects were observed for patients over 80 years old.

Conclusion: Compared with no treatment, IV tPA treatment in WUS patients was associated with improved clinical outcomes and reduced mortality without an increased risk of adverse effects. These findings support the consideration of tPA for WUS within the specified treatment window.

Keywords: Ischemic Stroke, Wake-up Strokes, Tissue Plasminogen Activator, Treatment Outcome, Safety

1. Introduction

Stroke is the greatest cause of mortality globally, with around 140,000 stroke fatalities and 800,000 new strokes occurring each year in the US alone (1). Indeed, many surviving patients have long-term disability and low quality of life. Patients with acute ischemic stroke (AIS) symptoms should receive intravenous tissue plasminogen activator (IV tPA) prior to four-and-a-half-hour window time with this class of medications, which includes alteplase, reteplase, and Tenecteplase, according to the most recent stroke therapy protocols and guidelines (2).

Among all the AIS incidences, nearly 14–29.6% are related to the wake-up stroke (WUS) and unknown time stroke. In WUS, the exact time of stroke incidence is unknown, and stroke can occur during sleep. Therefore, in the first evaluation, WUS treatment by tPA is forbidden because the incidence time is unknown (3). Despite all of

the promising results of using tPA in WUS patients, the use of this drug in these patients is performed with caution. The defined guidelines for treating these patients have not been introduced, and there are no clear indications or contraindications. Indeed, tPA therapy in older people with AIS is crucial and requires more attention because of the increased risk of adverse effects. Previous studies have shown that the risk of ICH after the use of tPA increases by 4.9% in patients over 55 years of age and 10.3% in those over 75 years of age. Furthermore, additional research has shown that the incidence of ICH in people over 80 is 10%–13% higher than previously reported (4, 5). Therefore, tPA treatment at these ages is essential.

In this investigation, we thus assessed IV tPA in WUS patients at unknown periods to ascertain the safety and effectiveness of therapy based on the mismatch between DWI-FLAIR in MR images, and we followed up with patients to assess the treatment's effectiveness after three months.

2. Materials and Methods

2.1 Study Design and Setting

This study is a single-center, open-label clinical trial conducted at the Vali-e-Asr Hospital Stroke Care Unit (SCU) in Zanjan, Iran. The hospital has been recognized with multiple Diamonds State Awards by the Angle European Stroke Organization (ESO) and the Angle World Stroke Organization (WSO) between 2018 and 2023 and was designated a top center for intravenous thrombolysis (IVT) and acute phase protocols by SITS International in 2019, 2020, and 2022.

2.2 Participants

A total of 107 patients with wake-up stroke (WUS) were enrolled and divided into two groups: 53 patients who received intravenous tissue plasminogen activator (IV tPA) and 54 patients who did not receive thrombolysis. The inclusion criteria were acute neurological symptoms consistent with stroke upon awakening, presentation within four hours of symptom onset, age ≥18 years, and a diagnosis of acute ischemic stroke, confirmed as either wake-up stroke or of unknown onset.

The exclusion criteria included intracranial hemorrhage on CT or MRI, a modified Rankin scale (MRS) score >2 prior to stroke, contraindications to MRI, infarction exceeding one-third of the midbrain artery or more than 100 ml, conditions increasing bleeding risk (e.g., severe microangiopathy, thrombocytopenic purpura), age <18 years, pregnancy, recent stroke (within three months), history of symptomatic intracranial hemorrhage, use of anticoagulants or thrombolytic agents within 48 hours, platelet count <100,000, blood glucose levels <50 or >400 mg/dL, uncontrolled blood pressure, inherited or acquired hemorrhagic disorders, recent gastrointestinal or urinary bleeding, acute pancreatitis, severe liver disease, active bleeding in noncompressible areas, recent major surgery, head injuries, delays in MRI or treatment initiation, and absence of lesions in diffusion-weighted imaging (DWI).

2.3 Data collection

At admission, skilled neurologists evaluated the patients. Clinical evaluations comprised the MRS at discharge and three months after stroke, as well as the NIHSS at arrival and discharge. MRI sequences such as fluid-attenuated inversion recovery (FLAIR), SWI, T1-weighted imaging, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) were used in imaging investigations. CT scans were conducted 24 hours following the injection of tPA or in the event of a headache, hypertensive crisis, or clinical deterioration. On average, it took 43.06 minutes from the start of symptoms until the injection of tPA.

2.4 Statistical analysis

SPSS version 26.0 (IBM, NY, USA) was used to analyze the data. Whereas categorical variables are given as proportions or frequencies, continuous variables are reported as means with standard deviations or medians with interquartile ranges based on data distribution. When necessary, statistical comparisons were made using the chi-square test, independent t test, paired t test, Mann-Whitney U test, and Fisher's exact test.

To evaluate the efficacy of tPA, binary logistic regression analysis was performed with the untreated tPA group as the reference category. The outcomes included functional independence, excellent functional outcomes, and mortality at discharge and three months. Ordinal logistic regression was used to assess the distribution of mRS scores at 90 days. All analyses were adjusted for baseline characteristics, including age, sex, ischemic heart disease, stroke history, diabetes mellitus, hypertension, atrial fibrillation, smoking, hyperlipidemia, and the NIHSS score. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported, with statistical significance set at a p value of <0.05.

3. Results

With respect to patient demographic characteristics, 107 WUS patients and patients at unknown times were included in this cohort study, of which 53 samples (49.5%) were treated with tPA and 54 samples (50.5%) were not treated with tPA. The admission NIHSS score was significantly higher in the untreated group [12.5 (8–17.3) vs. 10 (5.5–15)]. However, the other demographic features, such as ischemic heart disease, a history of stroke, diabetes mellitus, hypertension, a history of atrial fibrillation, smoking, hyperlipidemia, and the NIHSS score at admission, were not significantly different between the two groups. Table 1 summarizes the baseline characteristics of the patients in each group.

Various factors are evaluated in terms of clinical outcome (Table 2). The NIHSS score at admission was greater in the untreated group [12.5 (8–17.3) vs. 10 (5.5–15)], but the NIHSS score at discharge was significantly lower in the tPA-treated group. The discharge NIHSS

score in the treated group was 4.51 (5.27), whereas it was 6.98 (3.75); in untreated group. Thus, the treatment had a greater impact on the patients (p=0.006).

In terms of the incidence of ICH, two patients in the tPA group experienced ICH, but none of the nontPA-treated patients experienced this side effect. However, a significant difference in the incidence of ICH as the main side effect was not found between tPA-treated and nontPA-treated patients (P=0.243).

In terms of mortality, in-hospital mortality was lower in the treated group, as in the treated group, two (3.8) patients died; however, in the untreated group, this number was 12 (22.2). Therefore, the treated group experienced significantly lower mortality (p=0.008). Indeed, after adjudication, the in-hospital mortality rate was considerably higher for untreated patients (OR = 6.56, 95% CI = 1.09–39.59; adjusted p = 0.040). (Table 3). Additionally, further analysis revealed a significantly lower total mortality rate (in-hospital + out-of-hospital mortality rate) in the treated group than in the control group [6 vs. 17 patients died (P=0.011)].

Regarding the mRS score, the results demonstrated that 49.1% of treated patients achieved favorable mRS scores at discharge. This number in the control group was reported to be 11.1% and was insignificant compared with that in the treated group. Therefore, at discharge, the group receiving the drug had a much better mRS score (p<0.001). Indeed, at the three-month follow-up, a comparison of the distribution of mRS scores at 90 days revealed a significant difference between two groups (P=0.011) (Figure 1). Interestingly, a substantial proportion of patients with mRS scores of 0–1 (indicating excellent function) and 0–2 (indicating functional independence) were detected in the treatment group (60.4% and 67.9%, respectively). The clinical outcomes of the groups are presented in Table 3. The untreated group had a lower proportion of excellent functional outcomes (mRS 0--1), with a significant difference after adjusting for baseline characteristics (OR = 0.24, 95% CI = 0.09--0.64; adjusted p = 0.004). The tPA-treated patients had mRS scores of 1.8 versus 3.2 in the untreated group, indicating good treatment .resultsIndeed, the excellent functional outcome three months later in the treated group was 60.4%, which was better than that in the untreated group (p = 0.001). Therefore, the discharge outcome and three-month follow-up were better in the treated group.

Furthermore, 20 patients were not treated with tPA and 21 patients were treated with it, according to the analysis of patients over 80 (Table 4). The outcomes and side effects of the treated and untreated groups above the age of 80 did not differ significantly.

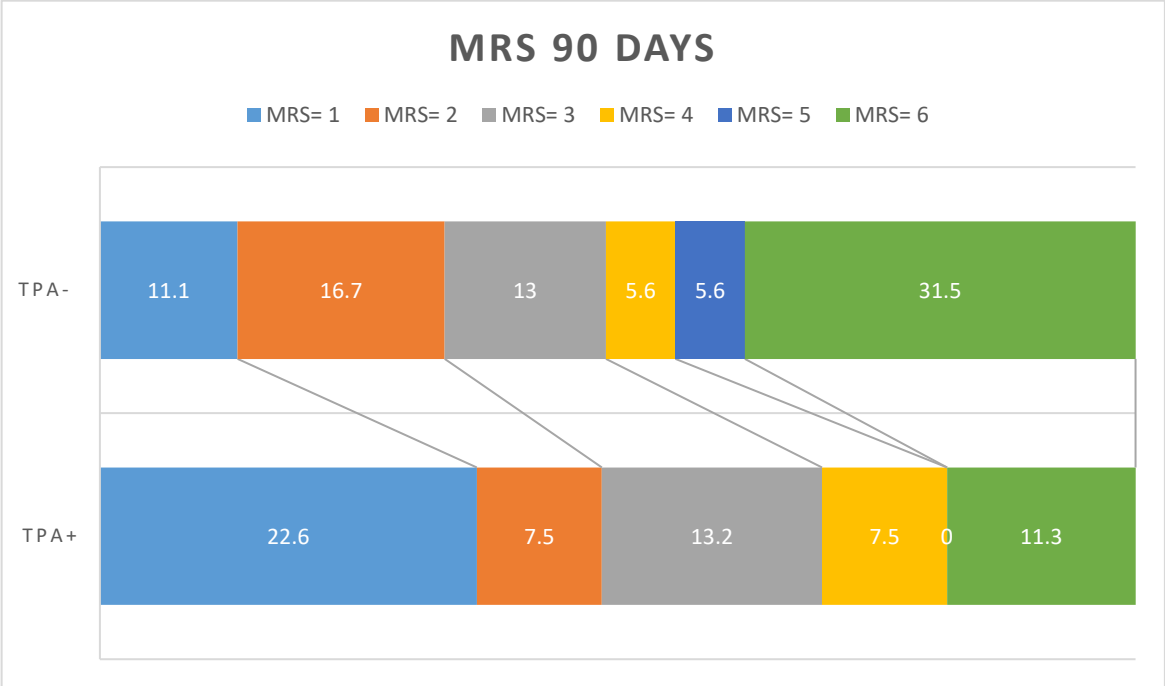

Figure 1. Comparison of the mRS score 90 days later in the group receiving venous thrombolysis. (tPA^+) with the group not receiving the drug (tPA^-).

Table 1. **Baseline characteristics of wake-up stroke patients.**

Variables	tPA^{+} (*N* =53)	tPA^{-} (*N* =54)	*P* value
Age, years [median (IQR)]	75(63-83)	75(62.75-84)	0.217
Gender, male [N (%)]	26(49.1)	23(42.6)	0.563
Ischemic heart disease [N (%)]	11(20.8)	10(18.5)	0.812
History of stroke [N (%)]	9(17)	15(27.8)	0.228
Diabetes mellitus [N (%)]	13(24.5)	20(37)	0.210
Hypertension [N (%)]	42(79.2)	47(87)	0.312
History of Atrial Fibrillation [N (%)]	5(9.4)	9(16.7)	0.391
Opium [N (%)]	0(0)	0(0)	N/A
Smoking [N (%)]	11(20.8)	7(13)	0.312
Hyperlipidemia [N (%)]	5(9.4)	5(9.3)	1.000
Systolic blood pressure, mmHg [mean (SD)]	158.83(29.11)	152.48(22.77)	0.212
Diastolic blood pressure, mmHg [median (IQR)]	90(80-95)	90(80-90)	0.636
Blood sugar, mg/dl [median (IQR)]	114(98-158)	135.5(106-189.3)	0.217
NIHSS score [median (IQR)]	10(5.5-15)	12.5(8-17.3)	0.013
Days of hospitalization [median (IQR)]	5(3-11)	5(3-7)	0.221

Data are n/N (%), mean (standard deviation), or median (interquartile range).
tPA$^{+/-}$, tissue plasminogen activator receiver or not; NIHSS, National Institutes of Health Stroke Scale.
The P value indicates a comparison between groups.

Table 2. Efficacy and safety outcomes in two groups of wake-up stroke patients.

Outcomes	tPA^{+} (*N* =53)	tPA^{-} (*N* =54)	*P* value
mRS 0-1 at 90 days [N (%)]	32(60.4)	15(27.8)	0.001
mRS 0-2 at 90 days [N (%)]	36(67.9)	24(44.4)	0.019
mRS distribution at 90 days			
0 [N (%)]	20(37.7)	9(16.7)	0.011
1 [N (%)]	12(22.6)	6(11.1)	
2 [N (%)]	4(7.5)	9(16.7)	
3 [N (%)]	7(13.2)	7(13)	
4 [N (%)]	4(7.5)	3(5.6)	
5 [N (%)]	0(0)	3(5.6)	
6 [N (%)]	6(11.3)	17(31.5)	
ICH [N (%)]	2(3.8)	0(0)	0.243
NIHSS score discharge [mean (SD)]	4.51(5.21)	6.98(3.75)	0.006
In-hospital death [N (%)]	2(3.8)	12(22.2)	0.008
Out-of-hospital death [N (%)]	4(7.5)	5(9.3)	1.000
Total death [N (%)]			0.011

tPA$^{+/-}$, tissue plasminogen activator receiver; mRS, modified Rankin scale; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale. The P value indicates a comparison between groups.

Table 3. **Efficacy and safety outcomes between two groups of wake-up stroke patients.**

Outcomes	tPA^{+} (*N* =53)	tPA^{-} (*N* =54)	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
mRS 0-1 at 90 days [N (%)]	32(60.4)	15(27.8)	0.25(0.11-0.57)	0.001	0.24(0.09-0.64)	0.004
mRS 0-2 at 90 days [N (%)]	36(67.9)	24(44.4)	0.38(0.17-0.83)	0.015	0.41(0.16-1.05)	0.062
ICH [N (%)]	2(3.8)	0(0)	N/A	N/A	N/A	N/A
In-hospital death [N (%)]	2(3.8)	12(22.2)	7.29(1.54-34.38)	0.012	6.56(1.09-39.59)	0.040
Out-of-hospital death [N (%)]	4(7.5)	5(9.3)	1.25(0.32-4.94)	0.750	0.89(0.19-4.17)	0.883
Total death [N (%)]	6(11.3)	17(31.5)	0.28(0.1-0.78)	0.014	0.3(0.09-1.03)	0.056

tPA$^{+/-}$, tissue plasminogen activator receiver; mRS, modified Rankin scale; ICH, intracranial hemorrhage; OR, odds ratio.

Table 4. **Efficacy and safety outcomes in two groups of wake-up stroke patients older than 80 years.**

Outcomes	tPA^{+} (*N* =21)	tPA^{-} (*N* =20)	*P* value
mRS 0-1 at 90 days [N (%)]	10(47.6)	4(20)	0.062
mRS 0-2 at 90 days [N (%)]	11(52.4)	6(30)	0.146
mRS distribution at 90 days			
0 [N (%)]	6(28.6)	2(10)	0.380
1 [N (%)]	4(19)	2(10)	
2 [N (%)]	1(4.8)	2(10)	
3 [N (%)]	5(23.8)	3(15)	
4 [N (%)]	1(4.8)	1(5)	
5 [N (%)]	0(0)	1(5)	
6 [N (%)]	4(19)	9(45)	

ICH [N (%)]	2(9.5)	0(0)	0.157
NIHSS score discharge [mean (SD)]	5.24 ± 6.12	6.75 ± 2.75	0.312
In-hospital death [N (%)]	2(9.5)	7(35)	0.0٦٧
Out-of-hospital death [N (%)]	2(9.5)	2(10)	0.959
Total death [N (%)]	4(19)	9(45)	0.074

$tPA^{+/-}$, tissue plasminogen activator receiver; mRS, modified Rankin scale; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale. The P value indicates a comparison between groups.

4. Discussion

In this study, we examined the efficacy and safety of tPA treatment in WUS patients and compared these factors with those of other standard patients. In addition, we separately analyzed the number of patients over 80 years of age with WUS to determine their tPA efficacy.

Our results showed that the utilization of IV tPA as a primary treatment in patients with WUS improves treatment, reduces disability, increases independent living, and reduces mortality in many patients. The most critical factors for this comparison were the evaluation of the NIHSS score and mRS score in terms of effectiveness, the rate of ICH and significant bleeding in other organs, and mortality in terms of safety. Our study revealed no significant differences between the tPA and control groups at the time of admission in terms of previous disability (mRS at baseline), demographic, or risk factors. In terms of the NIHSS score, the tPA-treated group had a lower NIHSS score at discharge, so the treatment group had a better outcome on the basis of this indicator. Our study revealed significant differences in the mRS score. Indeed, the mortality results for WUS and unknown durations revealed considerable reductions in in-hospital and total mortality. Although these findings reveal substantial results for IV tPA therapy in WUS patients, further investigations of the safety and efficacy of this treatment in WUS patients are needed.

Previous studies presented that the efficacy of IV tPA drugs is completely time-dependent and that thrombolysis should be infused less than four and a half hours from the onset of symptoms, which requires knowing the time of onset of symptoms or the last time the patient is asymptomatic (6). Numerous studies have shown that in patients with AIS with Penumbra syndrome, thrombolysis significantly increases the blood flow retention to the ischemic part, decreases the growth of the ischemic area, and improves clinical outcomes. For this reason, time is essential in AIS (7). However, 25% of stroke patients who experience WUS at unknown times do not have a precise starting time for stroke, have some challenges in therapy, and are excluded from receiving thrombolytic (8).

For the judgment and diagnosis of AIS, various imaging methods, such as CT or MRI, was used. To compare the effects of CT and MRI approaches on IV tPA, a study investigated the differences in outcomes between WUS patients. In this study, 100 patients received IV tPA-based CT scans, and 84 patients received drugs on the basis of evidence from MRI scans. The baseline data, such as severity or admission time, were similar between the diagnostic imaging methods. With respect to CT, the door-to-needle time was shorter at 45 minutes than at 75 minutes (with a mean difference of 28 minutes). There were no significant differences in factors such as favorable outcomes, ICH, or adjusted odds ratios (9). In another study in this field, researchers studied the efficacy of MRI-based FLAIR-mismatch and CT-based net water uptake (NWU). The 50 patients were evaluated with both imaging modalities 0.5–8 hours after symptom onset. The average time between imaging MRI and CT was 35 minutes; as a result, the diffusion-weighted imaging (DWI)-FLAIR mismatch accuracy was 68.8%, the sensitivity was 58%, and the specificity was 82%. The accuracy of NWU in the CT scan was 85%, the sensitivity was 91%, and the specificity was 78%. Among the patients, 46 (53%) of the 87 whole WUS patients demonstrated low NWU. Therefore, NWU seems to be a better option than MRI with low NWU in WUS patients. Therefore, a CT scan is a better option than an MRI scan for accelerating the response, performance, and number of results (10).

However, previous studies have demonstrated the valuable benefits of DWI-FLAIR imaging in predicting the use of IV tPA in WUS patients with the exact

incidence of sICH (11). Studies have shown that a mismatch between DWI and FLAIR helps to estimate the onset time of stroke in patients whose precise time of onset of symptoms is unknown. DWI-FLAIR mismatch indicates infarction within four and a half hours and the possibility of thrombolytic treatment (12-14). Huisa et al reported that many patients with ischemic stroke occurring at night indefinitely have FLAIR-DWI mismatch, indicating the recent onset of symptoms (15). Therefore, the use of MRI with FLAIR-DWI is an approved approach for diagnosing WUS patients.

On the other hand, many previous studies have evaluated the safety and efficacy of IV tPA in WUS patients and achieved various results (16). Nagai et al, in a study of 163 patients with WUS, concluded that approximately 30% of these patients could be candidates for tPA on the basis of negative FLAIR results (17). In a systematic review, the efficacy and safety of IV tPA evaluated and compared with those of placebo (normal saline) or nontreatment-based imaging algorithms. In this study, 14,017 patients were enrolled, and 12.5% (1,757) received IV tPA from MRI, CT, and combination findings. Sixty-one percent of IV tPA-treated patients achieved a 0–2 mRS score at 90 days; the relative risk was 1.21 compared with that of non-IV tPA-treated patients, and the incidence of sICH after 36 h was 3%. Therefore, similar to our study, this survey suggested IV tPA in WUS patients because of better outcomes 90 days after administration (18).

Another study was carried out on IV tPA in WUS patients to evaluate the efficacy and safety of this treatment in the Austrian Stroke Unit included 107,895 stroke patients, including 12,534 WUS patients and 91,899 precise-time stroke patients. Among the patients, 7.2% (904) had WUS, and 18.2% of the other patients received IV tPA. With this method, WUS patients who received IV tPA had twofold higher initial NIHSS scores than other patients did (eight versus four). The WUS patients' outcomes did not differ from those of different people, and the sICH rate did not significantly differ (4.1% versus 4%). Therefore, IV tPA has the same efficacy and safety in WUS patients and other patients (19). Like this study, our survey revealed no difference in the incidence of ICH between tPA-treated and untreated patients. Nevertheless, our study demonstrated better outcome factors in addition to these factors.

As we mentioned, some therapeutic methods, such as thrombectomy, may be good substitutes for IV tPA. Nevertheless, it must be noted that this treatment requires advanced hospitals with well-experienced teams, while some studies have shown the same results between IV tPA and thrombectomy (20, 21). Indeed, some studies did not find a better thrombectomy outcome with tPA than with IV tPA. For example, one study investigating the effect of IV tPA on WUS patients revealed that after 90 days of IV tPA, 66% treatment efficacy was achieved in WUS patients versus 58% in other patients, with a 1.13 risk ratio and 95% confidence interval. While endovascular thrombectomy of large vessels has 46% treatment efficacy for WUS after 90 days, IV tPA has better outcomes than thrombectomy (22).

Additionally, tPA-based MRI evidence was used to detect SARS-CoV-2 viral infection in WUS patients 6–5 h after they were suspected to be in a healthy state. After administration, MRI revealed a lower stroke burden without evidence of sICH. Therefore, the MRI protocol may be used in WUS patients with SARS-CoV-2 (23). With respect to drugs, some studies have used tenecteplase as an alternative to alteplase, but recent studies have not shown any overcommitment in WUS between these drugs, and the results have shown the same outcomes (24, 25). In addition, for these subjects, the treatment of those over 80 years of age was performed separately from that in our study, but unfortunately, significant results were not achieved. Perhaps the small number of patients was responsible for the lack of significance of the results. Therefore, more information and data are needed to draw more conclusions in this regard, which hopefully will be done in the future and presented as unique guidelines. A recent investigation reported excellent outcomes of tPA therapy in elderly AIS patients. Nevertheless, these results require evaluation of WUS and elderly patients at unknown times, especially to obtain the latest results (26, 27).

Limitation

With respect to this study's limitations, we encounter several barriers. First, the analysis of those over 80 years of age revealed no significant results related to the small sample size. Second, the risk factors and related subjects' quality and validity are challenging with any registry-based research, and selection bias (i.e., not registering all patients with all outcomes) may occur; thus, registry data must be analyzed cautiously. Third, the lack of accurate information about the door-to-needle time is due to the long duration of the MRI, or sometimes, it is performed in another center, making it difficult to adjust this issue accurately. Fourth, this survey was the first in Iran to investigate all outcomes, such as mortality, discharge outcome, ICH, and three-month follow-up, so more surveys are needed to prove the results. Finally, this type of treatment has not been universally accepted by other colleagues in other fields of medicine. Therefore, sometimes, it is difficult to satisfy some patients with this type of treatment, considering the consequences of the work, which requires more investigation in this field.

5. Conclusion

This study demonstrated that tPA treatment in patients with wake-up stroke (WUS) significantly improved clinical outcomes, including reduced

disability and lower mortality rates, compared with those of patients not treated with tPA. Despite the lack of significant differences in adverse effects, such as intracerebral hemorrhage, between the two groups, tPA-treated patients had better functional outcomes and lower mortality. Our findings align with previous research supporting the efficacy of tPA in stroke patients, even in the absence of a precise symptom onset time. However, limitations such as small sample sizes and variability in data collection highlight the need for further research to validate these results and address treatment efficacy in elderly populations and specific subgroups.

6. Declarations

6.1 Acknowledgments

The authors thank the SITS International Organization for assisting in the collection of appropriate data. Indeed, thanks to the Vali-e-Asr Hospital personnel for trying to save lives, especially the doctors, residents, and nurses in the stroke care unit department and neurology ward.

6.2 Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Ethics Committee of Zanjan University of Medical Sciences (Code IR.ZUMS.REC.1398.291). Informed consent was obtained from all participants, and all communications were recorded in the SITS system.

6.3 Authors' Contributions

A.G. Conceptualization, Writing-review and editing, and Supervision. H.N. Methodology, Writing-original draft preparation, and writing-review and editing. F.K. Conceptualization, Investigation, Writing-review and editing, and Project administration. K.H. Investigation, Data curation, Resources, Writing-original draft preparation, and Writing-review and editing.

6.4 Conflict of Interest

The authors declare no conflict of interest regarding the publication of this study.

6.5 Fund or Financial Support

We sincerely thank Babol University of Medical Sciences for their financial support.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

6.7 Data availability statement

The data supporting this study's findings are available upon request from the corresponding author.

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