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Research Article

# Examination of Treatment Options According to Clinical Features and Radiological Findings in Wake-up Stroke

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**Abstract**

**Aim:** Wake-up stroke patients account for one-fifth of all ischemic stroke patients and they have been deprived of recanalization treatment as the onset of the stroke is not known. It has come into the focus of recent research that this treatment could be applied to particularly patients who are selected on a radiological basis. We aimed to examine clinical and demographic characteristics of wake-up strokes.

**Material and Methods:** All ischemic stroke patients who presented to the emergency service throughout the night were analyzed. Patients with wake up stroke were recorded. The time of finding these patients, clinical features, treatment options and mortality status of these patients were examined. It was examined whether they received intravenous thrombolysis (IVT), endovascular therapy (EVT), or both as acute reperfusion therapy.

**Results:** Age, gender, the last time when they were seen healthy, treatment start time, treatment types, clinical classification, comorbid diseases, and discharge status of 72 wake-up stroke patients were analyzed. It was found that the time of discovery of 51.4% (n=37) of the wake-up stroke patients was 06.00 am and afterwards. Of these patients, 15.3% (n=11) received intravenous tissue plasminogen activator and/or endovascular treatment. These patients' hospital stay durations, intracerebral hemorrhage status following the procedure, NIHSS scores, angiography findings, and mortality rates were examined. Here, mortality rate was found to be significantly high especially in patients with high NIHSS score.

**Conclusion:** Wake-up stroke is more common in the period close to the time of waking up in the morning. Recanylazation therapy should always be considered as an option in these patients.

**Keywords:** Wake-up stroke, circadian rhythm, intravenous tissue plasminogen activator, endovascular treatment, NIHSS

## INTRODUCTION

Cerebrovascular diseases (CVD) occur as a result of an occlusion or rupture in brain vessels. Poor blood flow in the brain tissue results in cell death (1). Cerebrovascular diseases are the leading causes of death in both genders worldwide (2). It is also one of the causes of disability in adults (3). There are some risk factors for stroke. These risk factors can be counted as diabetes mellitus (DM), atrial fibrillation (AF), hypertension (HT), transient ischemic attack and carotid stenosis (4).

According to the World Health Organization (WHO), it is estimated that 5.4 million individuals worldwide in 2000 and approximately 6.2 million individuals worldwide in 2015 lost their lives due to CVDs (2). In the USA, stroke was one of the leading causes of death in both sexes in 2015 (5). Stroke is in second place among the leading causes of death in Europe and accounted for the death of nearly 1 million individuals in 2015. This constitutes approximately 14% of female deaths and 9% of male deaths (6).

Ischemic stroke accounts for 80% of all strokes (7). Wake-up stroke constitutes 25-30% of all ischemic stroke cases (8). Intravenous thrombolysis and thrombectomy are significant treatment methods which have positive effects on mortality and morbidity in ischemic stroke patients (9,10). Unknown time of symptom onset in wake-up stroke patients is important in terms of thrombolysis and thrombectomy treatment opportunity (11). While deciding on the treatment type, rather than depending on time, making a decision on the basis of individual patients may provide more patients with treatment opportunity (12).

In the study, relationship of symptom time of especially wake-up strokes with circadian rhythm and their clinical

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and demographic characteristics, and patient-based treatment options and progression rather than being time-dependent were examined.

## MATERIAL AND METHOD

### Study Data Collection

Study ethical approval was obtained with the decision numbered 2021/88 and dated 13.10.2021 from Malatya Turgut Özal University Clinical Research Ethics Committee. In the study, patients who were diagnosed with ischemic stroke in the emergency service of Malatya Education and Research Hospital between January 2019-June 2021 were retrospectively examined over the hospital's automation system. Based on their clinical characteristics at admission, the patients were classified according to Oxfordshire Community Stroke Project (OCSP) classification system as Total Anterior Circulation Infarction (TACI), Partial Anterior Circulation Infarction (PACI), Posterior Circulation Infarction (POCI) and Lacunar Infarction (LACI). Among the ischemic stroke patients who presented to the emergency service (door time) between pm 11:00-am 11:00, those with wake-up stroke were included in the study. Patients with ischemic stroke but not wake-up stroke and patients with hemorrhagic stroke were not included in the study. The last time when the patient was seen healthy (witness), time of presentation to the emergency service, radiological imaging time, and treatment start time were recorded. First of all, the wake-up patients' age, gender, clinical classification, comorbid diseases, treatment options, and mortality status were examined. Acute reperfusion treatments have been classified as intravenous thrombolysis (IVT), endovascular treatment (EVT), and combined use of these two treatments. National Institutes of Health Stroke Scale (NIHSS) scores, hospital stay durations, angiography findings, intracerebral hemorrhage status after procedure, and discharge status of the wake-up stroke patients whose computerized tomography findings were normal or close to normal were examined. These patients were divided into subgroups according to their mortality status, and risk factors were analyzed.

### Statistical Analysis

SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL) 22 package software was used. Descriptive data were expressed as number (n) and percentage (%) values for categorical variables, while they were presented as mean±standard deviation (mean±SD) for continuous variables. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables. Compliance of continuous variables with normal distribution was evaluated through Shapiro-Wilk test. Student's t test was employed in pairwise comparison of the groups. $p<0.05$ was accepted significant.

## RESULTS

72 patients in total, 42 (58.3%) of whom were male and 30 (41.7%) of whom were female, were included in the study. The mean age of the participants was found as 71.8±12.7 years (min-max=36-96/years). Of the patients, 61 (84.7%) received medical treatment, 3 (4.2%) IVT (intravenous thrombolysis), 3 (4.2%) EVT (Endovascular treatment), and 5 (6.9%) IVT+EVT. Regarding the OCSP classification of the patients, 14 (19.4%) were TACI, 29 (40.3%) were PACI, 15 (20.8%) were LACI, and 14 (19.4%) were POCI. 66.7% of the patients had HT, 27.8% had DM, 33.3% had AF, 41.7% had coronary artery diseases, and 30.6% had hyperlipidemia 26.4% of the patients died (Table 1).

**Table1. Characteristics of the patients included in the study (n=72)**

| | | Number | % |
|---|---|---|---|
| Gender | Male | 42 | 58.3 |
| | Female | 30 | 41.7 |
| Age, Mean±SD | | 71.8±12.7 | |
| Treatment | Medical | 61 | 84.7 |
| | IVT | 3 | 4.2 |
| | EVT | 3 | 4.2 |
| | IVT+EVT | 5 | 6.9 |
| OCSP classification | TACI | 14 | 19.4 |
| | PACI | 29 | 40.3 |
| | LACI | 15 | 20.8 |
| | POCI | 14 | 19.4 |
| Comorbid diseases* | HT | 48 | 66.7 |
| | DM | 20 | 27.8 |
| | AF | 24 | 33.3 |
| | CAD | 30 | 41.7 |
| | HL | 22 | 30.6 |
| Status | Discharged | 53 | 73.6 |
| | Dead | 19 | 26.4 |

*There are patients who had more than one comorbid diseases
EVT: endovascular treatment, IVT: intravenous thrombolysis, OCSP: Oxfordshire Community Stroke Project, TACI: total anterior circulation infarction, PACI: partial anterior circulation infarction, POCI: posterior circulation infarction, LACI: lacunar infarction, HT: hypertension, DM: diabetes mellitus, AF: atrial fibrillation, CAD: coronary artery disease, HL: hyperlipidemia

While 61 (84.7%) of the patients received medical treatment, the remaining 11 (15.3%) patients received acute treatment. The characteristics of the patients who received acute treatment are presented in Table 2.

The last time when the patients were seen healthy, the time of discovery of the patients, and hospital presentation times of the patients were examined. When the discovery times of the patients were divided into three groups according to circadian rhythm as 23:00-03:00, 03:00-06:00, 06:00 and afterwards (n=11 [15.3%], n=24 [33.3%] and n=37 [51.4%], respectively), it was determined that 51.4% (n=37) of the patients were discovered at 06:00 and afterwards. 63.7% (n=7) of the patients receiving acute treatment were discovered after 06.00.

**Table 2. Characteristics of the patients who received acute treatment**

| Case | Gender | Age | NIHSS | OCSP classification | Treatment | CT angiography | Hemorrhage | Hospitalization duration (day) | Mortality |
|---|---|---|---|---|---|---|---|---|---|
| **1** | Male | 66 | 14 | TACI | EVT | LEFT ICA OCCLUSION OVER 80% | No | 12 | No |
| **2** | Female | 45 | 11 | TACI | IVT+EVT | RIGHT MCA TOTAL OCCLUSION | No | 6 | No |
| **3** | Female | 78 | 17 | PACI | IVT+EVT | NORMAL | Yes | 3 | Yes |
| **4** | Female | 80 | 20 | TACI | IVT | LEFT MCA OCCLUSION OVER 90% | No | 10 | Yes |
| **5** | Male | 75 | 13 | PACI | IVT+EVT | LEFT MCA TOTAL OCCLUSION | Yes | 29 | No |
| **6** | Male | 53 | 8 | LACI | IVT | LEFT ICA NEAR-TOTAL OCCLUSION | No | 3 | No |
| **7** | Male | 79 | 21 | PACI | IVT+EVT | RIGHT MCA BRANCH TOTAL OCCLUSION | Yes | 106 | Yes |
| **8** | Male | 78 | 13 | TACI | IVT+EVT | RIGHT MCA TOTAL OCCLUSION | Yok | 15 | Yes |
| **9** | Female | 68 | 20 | PACI | EVT | LEFT MCA TOTAL OCCLUSION | Yok | 56 | No |
| **10** | Male | 48 | 20 | PACI | EVT | LEFT VA OCCLUSION OVER 70% | Yok | 61 | Yes |
| **11** | Male | 78 | 12 | POCI | IVT | NONE | Yok | 8 | No |

NIHSS: National Institutes of Health Stroke Scale, OCSP: Oxfordshire Community Stroke Project, EVT: endovascular treatment, IVT: intravenous thrombolysis, CT: computer tomography, ICA: internal carotid artery, MCA: middle cerebral artery, VA: vertebral artery

It was observed that there was no significant gender difference between those who received medical treatment and those who received acute treatment. Who received medical treatment, 57.4% were male. Who received acute treatment, it was seen that 63.6% of them were male (p=0.753). While the mean age of the patients who received medical treatment was 72.5±12.6, the mean age of the patients who received acute treatment was 68.0±13.3, and no significant difference was found in terms of age (p=0.443). When the mortality was examined, it was observed that there was no significant difference between those who received medical treatment and those who received acute treatment (23%, 45.5%, respectively, p=0.145). No statistically significant difference was determined between the treatment groups in terms of other parameters (p>0.05) (Table 3). CT angiography examination was performed on 10 of the wake-up stroke patients who received acute treatment, and major blood vessel occlusion was detected in 9 patients.

**Table3. Comparison of the characteristics of the patients according to treatment groups**

| | | Medical treatment (n=61) | | Acute treatment (n=11) | | p* |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| **Gender** | **Male** | 35 | 57.4 | 7 | 63.6 | 0.753 |
| | **Female** | 26 | 42.6 | 4 | 36.4 | |
| **Age, Mean±SD** | | 72.5±12.6 | | 68.0±13.3 | | 0.443** |
| **OCSP classification** | **TACI** | 10 | 16.4 | 4 | 36.4 | 0.384 |
| | **PACI** | 24 | 39.3 | 5 | 45.5 | |
| | **LACI** | 14 | 23.0 | 1 | 9.1 | |
| | **POCI** | 13 | 21.3 | 1 | 9.1 | |
| **Hypertension** | **Yes** | 41 | 67.2 | 7 | 63.6 | 0.817 |
| | **No** | 20 | 32.8 | 4 | 36.4 | |
| **Diabetes Mellitus** | **Var** | 18 | 29.5 | 2 | 18.2 | 0.716 |
| | **Yok** | 43 | 70.5 | 9 | 81.8 | |
| **Atrial Fibrillation** | **Yes** | 21 | 34.4 | 3 | 27.3 | 0.741 |
| | **No** | 40 | 65.6 | 8 | 72.7 | |
| **Coroner artery disease** | **Yes** | 26 | 42.6 | 4 | 36.4 | 0.753 |
| | **No** | 35 | 57.4 | 7 | 63.6 | |
| **Hyperlipidemia** | **Yes** | 19 | 31.1 | 3 | 27.3 | 0.797 |
| | **No** | 42 | 68.9 | 8 | 72.7 | |
| **Durum** | **Discharged** | 47 | 77.0 | 6 | 54.5 | 0.145 |
| | **Dead** | 14 | 23.0 | 5 | 45.5 | |

*Chi-square analysis, **Student's t test was applied, OCSP: oxfordshire community stroke project

When various parameters of 11 patients who received acute treatment were examined according to mortality status, NIHSS values of those who died were found to be significantly higher than NIHSS values of the patients who were discharged (p=0.045). 42.9% of the males and 50% of the females died, and no significant difference was found between the genders (p=0.819). Regarding dying, no significant difference was found in terms of age (p=0.238). As regards OCSP classification, while 50 % of those with TACI and 60% of those with PACI died. No patients with LACI and POCI died. No significant difference was found in OCSP classification in terms of mortality (p=0.547). 66.7% of those with hemorrhage and 37.5% of those without hemorrhage died, and no significant difference was determined between the two groups (p=0.545). Regarding dying, no significant difference was found in terms of hospitalization duration (P=0.342) (Table 4).

**Table 4. Comparison of various parameters of the patients who received acute treatment according to mortality status**

| | | Dead (n=5) | | Discharged (n=6) | | p* |
|---|---|---|---|---|---|---|
| | | Number | % | Percentage | % | |
| Gender | Male | 3 | 42.9 | 4 | 57.1 | 0.819 |
| | Female | 2 | 50.0 | 2 | 50.0 | |
| Age, Mean±SD | | 72.6±13.7 | | 64.2±12.7 | | 0.238** |
| OCSP classification | TACI | 2 | 50.0 | 2 | 50.0 | 0.547 |
| | PACI | 3 | 60.0 | 2 | 40.0 | |
| | LACI | 0 | .0 | 1 | 100.0 | |
| | POCI | 0 | .0 | 1 | 100.0 | |
| Hemorrhage | Yes | 2 | 66.7 | 1 | 33.3 | 0.545 |
| | No | 3 | 37.5 | 5 | 62.5 | |
| NIHSS, Mean±SD | | 18.2±3.3 | | 13.0±4.0 | | **0.045**** |
| Hospitalization Duration, Mean±SD | | 39.0±43.8 | | 19.0±20.3 | | 0.342** |

*Chi-square analysis, **Student's t test was applied, OCSP: oxfordshire community stroke project, NIHSS: National Institutes of Health Stroke Scale

## DISCUSSION

Wake-up stroke (WUS), which constitutes a significant portion of ischemic stroke patients, is defined as the stroke in which patients who do not have any anomalies before sleeping present with a newly developing neurological deficit when they wake up (13,14). One out of every five patients present with a wake-up stroke (15). Wake-up strokes have long been excluded from acute recanalization treatments due to their uncertain time of symptom onset. In studies conducted, the onset time of wake-up strokes has been reported to be the morning hours closest to the time of waking up (16,17).

In a study in which they examined circadian changes in acute ischemic stroke patients, it was reported that all stroke subtypes peaked between 06.00 a.m. and noon (18). Chaturvedi et al. also examined stroke subtypes and symptom onset times according to TOAST staging and demonstrated that all types concentrated relatively around early morning hours (19). In addition, when Serena et al. examined the clinical properties of strokes that occur during waking up and wakefulness, they could not find a distinct difference (20). In the present study, only the patients who presented to the hospital between 23:00-11:00 were examined, and especially wake-up stroke patients were tried to be determined. Acute ischemic stroke patients other than wake-up stroke patients were excluded from the study. In addition, the last time when they were seen healthy, discovery time, and hospital presentation time of the WUS patients were recorded. It was seen that especially the time of the patients waking up with a stroke was close to the waking up time of the circadian rhythm. When the patients were classified according to Oxfordshire Community Stroke Project (OCSP) staging which is based on clinical characteristics, there was no difference between those receiving medical treatment and acute treatment (21).

It is seen that acute ischemic stroke (AIS) patients are frequently faced with death, being bedbound, and needing others' help in the following periods (22). However, in the treatment of AIS, intravenous tissue plasminogen activator (IV t-PA), endovascular recanalization treatment, or combined use of these two procedures have significantly changed the course of the disease (23,24). Regarding the use of these treatments, symptom onset time and hospital arrival time in especially WUS patients are one the most important restricting factors (11). Still, it has been arguedin recent years that WUS patients can benefit from IV t-PA or endovascular reperfusion treatments (25,26). Especially in this group of patients, the applicability of these treatments by considering radiological imaging based diffusion-weighted and fluid-attenuated inversion recovery mismatch (Diffusion-FLAIR mismatch) has been evaluated (27-29).

The study conducted by Fink et al. in 2020 demonstrated that both clinical and multimodal MRI (magnetic resonance imaging) characteristics in wake-up strokes were not different from stroke patients with known symptom onset time. It was also recommended to research treatment

methods based on imaging parameters in these patients (30). In another study conducted, Barreto et al. included 40 WUS patients in the age range of 18-80 years, NIHSS ≤25, and based only on non-contrast CT imaging. They obtained 52.6% success modified RANKIN scores of 0 or 1 at the end of three months in these patients (31). In this study, patients aged 45-80 whose NIHSS scores were between 8-21, who did not have hypodensity in CT images, who had normal or close to normal CT findings, who mostly had major branch occlusion in CT, whose clinical and MR findings did not match were chosen.

It has also been stated that CT perfusion examination has an important place for radiological imaging based approach in WUS patients (32). In patients who were examined with CT and CT perfusion, many findings such as perfusion area-hypodensity mismatch, clinic-diffusion mismatch (DAWN criterion), diffusion-FLAIR mismatch (MR-Witness criterion), perfusion-diffusion mismatch (PDM criterion) have been used in the evaluation of wake-up stroke patients (17,33-35). As CT perfusion was not a radiological imaging technique routinely used in our hospital, some of these criteria could not be evaluated.

In 2011, Roveri et al. determined that patients who presented with wakefulness and wake-up strokes had similar disease characteristics and early ischemic changes, and they stated that early period WUS patients can benefit from thrombolytic treatment (36). Barreto et al. (2009) shared the data of 46 WUS patients who received IV t-PA (28 patients), intraarterial thrombolysis (14 patients), and combined treatment (4 patients). As a result of the study, they reported that thrombolysis treatment can be a reliable treatment option for WUS patients (25). In the double-blind, placebo-controlled randomized study they conducted (WAKE-Up Trial) in 2018, Thomalla et al. reported that iv-tPA treatment could be useful in selected patients (37). In this study, there was no significant difference between who received treatment and others in terms of age, gender, stroke subtype, and hospital stay. In addition, there was no significant difference the early mortality rates between the groups (p=0.145).

One of the most fatal complications seen after recanalization treatments is intracranial hemorrhages that may develop following the procedure. In one of the studies, although it had significant benefits in functional recovery outcomes following thrombolysis treatment, there was an increase in the risk of hemorrhagic complication, and there was no evidence showing that the treatment effect of alteplase decreased in ischemic stroke patients with ≥1 CMBs (cerebral microbleeds) (38). National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group found the risk of symptomatic intracerebral hemorrhage (SICH) as 6.4% in acute ischemic stroke patients who received IV t-PA (9). They also demonstrated that if National Institutes of Health Stroke Scale (NIHSS) score was >20 in these patients, SICH rate increased by 5-17% (39). SICH risk was found to have increased in wake-up stroke patients who received thrombolysis treatment compared to the control group (3%, 1%, respectively); however, this increase in hemorrhage risk did not have a significant effect on post-treatment functional outcomes (40). In this study, it was observed that there was no significant difference between intracranial hemorrhage rates in patients who received treatment according to their mortality status. However, the NIHSS scores of the patients who received treatment and died were significantly higher than the others (18.2±3.3, 13.0±4.0; p=0.045, respectively). This suggests that high NIHSS score is an important factor in terms of hemorrhage risk in patients after recanalization treatment applied.

In the present study, occurrence times, demographic and clinical properties, treatment choice, and the course of the disease regarding wake-up strokes, which constitute a significant portion of ischemic stroke cases, was reviewed in light of the literature.

### Limitations of Study

As the study had a retrospective design, the patients' long-term RANKIN scores and mortality rates could not be determined. Small number of patients, being a single-center study, and CT perfusion or FLAIR magnetic resonance imaging techniques not being in routine use in our emergency service are among the limitations of the study.

## CONCLUSION

Wake-up strokes continue to form a significant portion of acute ischemic stroke cases. It is thought that these patients, who constitute a significant group in terms of mortality and disability, should be examined in detail in terms of acute treatment options, and that radiological imaging based treatment options in selected patients should be evaluated. In addition, it is recommended to be careful with especially patients with high NIHSS score in terms of treatment failure.

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