

## Research Article

# Thrombolytic Therapy in “Wake up” Stroke: A One Year Single Centre Experience

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## Abstract

**Background:** Intravenous thrombolysis with alteplase was historically used to treat ischemic stroke only when symptoms onset was less than 4.5 hours. In 2018, October, New England Journal of Medicine (NEJM) published “WAKE UP Trial (WUT)”, which suggests benefit and safety of alteplase even for ischemic stroke with unknown time of onset and DWI/FLAIR mismatch detection at brain MRI. Since November 2018 a “WAKE UP Protocol (WUP)” was released in our hospital. The aim of our study is to report outcomes of patients included in WUP after one year since his institution.

**Methods:** We retrospectively identified all the patients enrolled for the “WUP” from November 2018 to October 2019 at university hospital of Sassari, Sardinia. “WUP” include patients with less than 80 years and with an acute ischemic stroke and unknown time of symptoms onset. They all underwent a CT scan and CTA that had to be negative for recent vascular lesions and for large intracranial vessels occlusion, and a MRI (DWI and FLAIR) in order to detect a DWI/FLAIR mismatch. If a restriction signal at DWI in association with no hyperintense signal of the same region on FLAIR was found, systemic thrombolysis (IVT) with alteplase was delivered.

**Results:** In total 33 patients were included in the “WUP”. Seventeen (51.5%) of them were males. Twenty-four patients had no thrombolysis; 17 (70.8%) because MRI showed a FLAIR hyper intensity, and 7 (29.2%) because a different diagnosis was made after MRI. Nine patients (27.3%) were treated with rTpa; two of them underwent mechanical thrombectomy after IVT. Only one of the alteplase patients had a mild haemorrhagic transformation of the ischemic lesion, not linked to a clinical worsening. No patient suffered recurrent ischemic stroke at 3 months. Modified Rankin Scale (mRS) at 3 months was 0 to 1 in 5 patients (55.5%), 2 in 3 patients (33.3%) and 4 in 1 patient (11.1%) in the IVT group.

**Discussion:** During the first year of “WUP” utilization, 33 patients have been enrolled and 9 of them (27.3%) underwent IVT. In “WUT”, after screening of 1362 patients, about 30% of them were randomized for rTpa or placebo. Even if in WUP, differently than WUT, a CT scan and a CTA was performed before MRI, we report no significant delay in MRI execution and treatment. Median time from symptoms recognition and thrombolytic therapy was indeed 3.1 hours in WUT and 3.2 hours in our experience. Only one patient who underwent IVT experienced a mild haemorrhagic transformation of the ischemic lesion, but he had no significant clinical worsening. No patient of the IVT group had a clinical worsening in terms of NIHSS score after therapy, and nobody of them had recurrent ischemic stroke at 3 months.

**Conclusions:** Our analysis, although the small sample size, confirm the evidence of benefit and safety of reperfusion treatment with alteplase in patients with ischemic stroke and unknown time onset, when a DWI/FLAIR mismatch was found at MRI.

**Keywords:** Thrombolytic therapy; Stroke; IVT

## Background

Ischemic stroke with an unknown time of onset (WAKE UP STROKE) were usually excluded from large trials assessing effectiveness and safety of rTpa [1,2], and they had traditionally a contraindication for revascularization therapies according to international guidelines [3]. Time of symptoms onset is unknown in about 14% to 27% of strokes [4], usually because neurological deficit is recognized when the patient awake from sleeping [5]. In May 2018 NEJM Thomalla’s publication “Magnetic Resonance Imaging (MRI) guided thrombolysis for stroke with unknown time of onset” report a

better functional outcome at 90 days in patients with wake up stroke who underwent intravenous alteplase, guided by a mismatch between Diffusion Weighted Imaging (DWI) and FLAIR (Fluid Attenuated Inversion Recovery) in the region of ischemia [6]. A visible diffusion restriction on DWI, in association with an absence of hyperintense signal in the same region on FLAIR is indeed a good predictor of symptoms onset within 4.5 hours before imaging [7].

This trial provided evidence of benefit in terms of functional outcomes in patients not eligible for endovascular reperfusion, who underwent reperfusion treatment with alteplase versus patients treated with placebo, despite numerically more deaths and significantly more patients with parenchymal haemorrhage in the alteplase group was found (findings similar to that in a pooled analysis of stroke thrombolysis trials).

In 2018 July, ISO (Italian Stroke Organization) provided a new recommendation about considering rTpa treatment for patients with Wake up stroke who catch “Wake up trial” inclusion criteria [8].

Thus, we report real world data from our single centre experience with a “Wake up stroke protocol” one year after his release.

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## Methods

We retrospectively identified all patients enrolled for the “wake up stroke protocol” in AOU Sassari Stroke Unit (an II level Stroke Unit serving about 450.000 people in the major hospital of the north of Sardinia) from November 2018 to October 2019. “Wake up stroke protocol” include patients aged less than 80 years old with a new neurological focal deficit with an unknown time of symptoms onset (exceptions were made for patients with more than 80 years with few or not comorbidity and mRS before stroke of 0 to 1). All patients arrived in hospital more than three hours since they were found symptomatic were excluded by protocol. All the enrolled patients underwent a basal CT scan and a CTA in order to excluded cerebral haemorrhage and occlusion of major intracranial arterial branches. When a proximal segment of Middle Cerebral Artery (MCA), Anterior Cerebral Artery (ACA) or the intracranial segment of the Internal Carotid Artery (ICA) was occluded, patient were not treated with IVT but transfer for endovascular treatment was arranged. If none of that occlusion was seen a brain MRI was performed and thrombolytic therapy (IVT) was given if a congruous visible restriction at DWI was seen, in association with no hyperintense signal of the same region on FLAIR. The entire patient treated with alteplase was admitted in SU, where EKG, BP and SpO<sub>2</sub> were monitored. They all underwent a neurological assessment and a NIHSS score was given before thrombolysis, 2 hours, and 24 hours after rT pain fusion and before discharge [9]. A CT scan was performed after 24 hours if patient clinically stable. No antithrombotic therapy was given in the 24 hours after rTpa. After 24 hours ASA or clopidogrel (or both) was given if CT scan didn't show haemorrhagic infarction [10], and a VTE prophylaxis was started if padua score >4 was calculate [11]. In patients with atrial fibrillation anticoagulant therapy (DOAC's or AVK) was started 3 to 6 or 12 days after symptom's onset depending by symptoms burden in terms of NIHSS scale and ischemic isodensity size at control CT scan [12]. Clinical outcome was obtained, for patients who underwent thrombolysis, after 3 months using the Modified Rankin Scale (mRs) and with NIHSS score assessment at discharge. Patients or their legal representatives provided written informed consent according to local regulation.

## Results

In total, 33 patients (17 male 51.5%, 16 Female 48.5%, mean age  $67.6 \pm 13.9$  years old) were enrolled in the “WUP” between November 2018 and October 2019. Demographic and baseline characteristics are shown in Table 1. Of those 33, 24 patients were excluded for IVT; 17 (70.8 %) because no mismatch on RMN imaging was detected (positive DWI with hyperintensity at FLAIR in the same region), and 7 (29.2%) because an alternative diagnosis was made after MRI. In 11 of the 26 strokes was involved left anterior circulation (42.3%), in 3 (11.5%) was involved right anterior circulation, and 12 (46.1%) were strokes of posterior circulation (Figure 1). The “wake up-emergency department Triage” mean time was 100 minutes; “Triage to MRI execution” median time was 82 minutes (24 to 168); “symptoms recognition to MRI” median time was 196.5 minutes (84 to 285). Nine patients (27.3%) were treated with rTpa; 2 (22.2%) of them underwent mechanical thrombectomy after IVT because of medical decision (very young patients with severe stroke symptoms). In those patients “wake up-IVT” median time was 200 minutes (134 to 290) with a “RMN-rTpa” median time from the beginning of RMN execution to the beginning of rTpa infusion of 61 (30 to 76) minutes (Table 2). Median NIHSS score at admission (before IVT) was 5 (3 to 19), while it was 2 (0 to 12) at the moment of SU discharge. NIHSS trends at

2 hours, 24 hours and discharge are shown in Graph 1. We report haemorrhagic transformation of the ischemic lesion, notlinked to a clinical worsening, only for one IVT patient. No patient suffered from recurrent ischemic stroke at 3 months. mRS at 3 months was 0 to 1 in 5 patients (55.5%), 2 to 3 in 3 patients (33.3%), 4 in 1 patient (11.1%) in the IVT group Graph 2. Before Stroke it was 0 in 8 patients and 1 in one patient (88.9% and 11.1%).

## Discussion

Any attempts previously made to show benefits and safety of thrombolysis for acute ischemic stroke beyond 4.5 hours failed, but in the last few years many efforts has been made in order to extend time window for revascularization therapies [13-15]; a modern advance consists in a image-guided approach (with second level imaging techniques) able to detect large penumbras areas potentially recoverable after revascularization. CT perfusion and MRI has been utilized in large trials to assess perfusion/diffusion mismatch with good outcomes [16]. Research of “salvable” brain tissue seems to be the new horizon of the revascularization therapies; this will lead to extend those treatments to “slow progress or” patients and people with unknown symptoms onset.

In the WAKE UP Trial (WUT) patients with stroke with unknown time onset had benefits after IVT when a DWI/FLAIR mismatch at MRI was found. After this publication, a WAKE UP Protocol (WUP) has been approved in our Hospital. In the first year of utilization 33 patients has been enrolled and 9 patients (27.3 %) underwent IVT. This data was consistent with WUT where 1362 patients underwent screening and about 30% was treated with rTpa or Placebo in the per-protocol population. In our court mean age was 67.6 years old, similar to the “WAT” mean age (65.3), 69% had arterial hypertension in our population versus 53% in “WUT”. More diabetic patients were included in “WUT” than in “WAP” (about 16% vs. 9%) although the high prevalence of Diabetes Mellitus in Sardinian population [17]. Patients with atrial fibrillation and with a history of previous Stroke were less represented in “WAT” than in “WAP” (respectively 11.7% vs. 21.2% and 14% vs. 21.2%). A high number of dyslipidemic patients were found in our population (63.3% vs. about 35% in “WUT”. Admission NIHSS median score were similar in both studies (5 in “WUP” vs. 6 in “WUT”). Differently from the “WUT”, all patients enrolled in “WUP” underwent MRI after a basal CT scan of the brain and a CTA; this approach differs from WAKE UP protocol, where no CT scan was performed and patients went straight to MRI study with multiple sequences (DWI, FLAIR, Echo gradient and TOF angiography of the circle of Willis), but it doesn't resulted in a substantial delay of thrombolytic therapy. Median time from symptoms recognition and thrombolytic therapy was indeed 3.1 hours in WUT and 3.2 hours in our experience. Some patients came to our hospital from others hospitals of the north of Sardinia by helicopter, and this is the cause for long “TRIAGE-RMN” time for patient 4 (Table 2). Two patients, both young (45 and 42 years old) and with severe strokes (respectively NIHSS score of 19 and 12), underwent IVT and mechanical thrombectomy afterwards. One of them hadan haemorrhagic transformation of the ischemic lesion without a clinical worsening in terms of NIHSS score at 24 h. No other IVT patient experienced haemorrhagic complications, no one had clinical worsening in terms of NIHSS score at 2.24 hours from IVT and at discharge from stroke unit, and no one of them had recurrent ischemic stroke at 3 months. mRS score at 3 months of patients excluded by protocol isn't available because a large part of them was lost at follow up. In “WUT” 53% of patients treated with alteplase had a mRs of 0 to 1 at 3 months; only

6.8% of patients had recurrent symptomatic ischemic stroke and 2% had a symptomatic intracranial haemorrhage at 3 months (Table 3). This study had several limitations, first of all the small sample size, in second line, we lost in follow up a large part of patients who didn't underwent IVT, because most of them were not admitted in Stroke Unit but in different ward (internal medicine, geriatric or neurology).

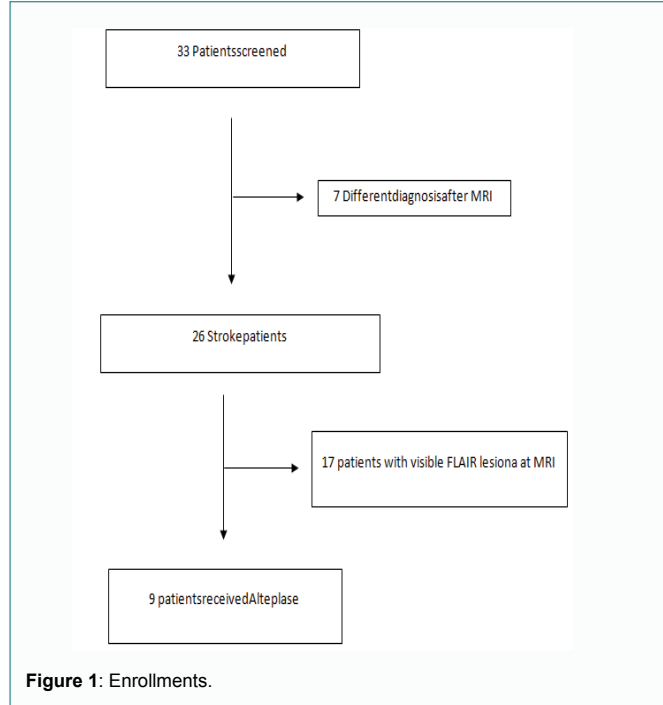
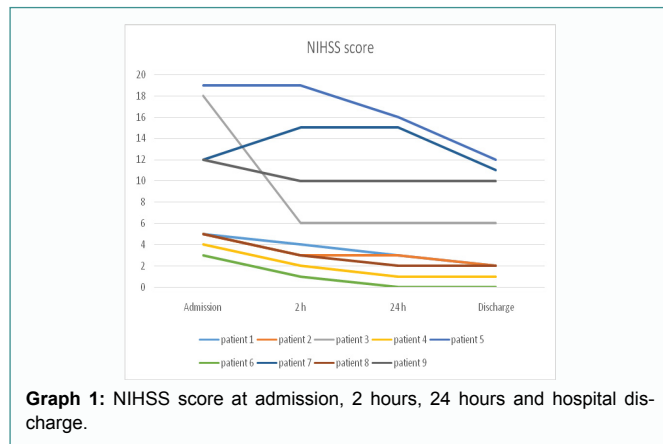
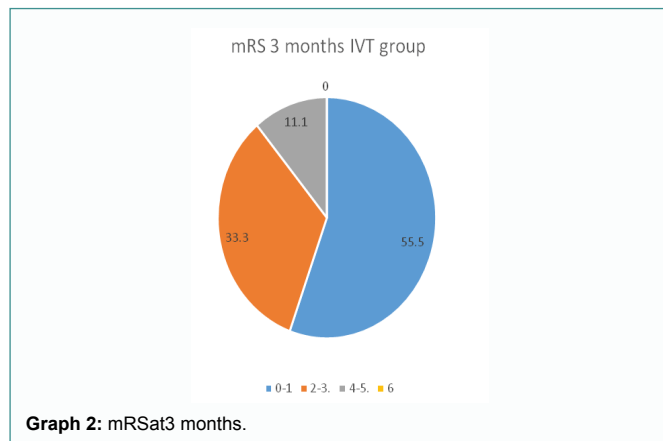


Figure 1: Enrollments.



Graph 1: NIHSS score at admission, 2 hours, 24 hours and hospital discharge.



Graph 2: mRS at 3 months.

Table 1: Population characteristics.

| Parameter                                    | Value total (33pz) | Value (no IVT) 24 | Value (IVT) 9 |
|--|--------------------|-------------------|---------------|
| N. males, n (%)                              | 17 (51.5)          | 14 (58.3%)        | 3 (33.3)      |
| Age (y), mean, SD ±                          | 67.6 ± 13.9        | 67.6              | 67.7          |
| Arterial Hypertension, n (%)                 | 23 (69.7)          | 15 (62.5)         | 6 (66.6)      |
| Diabetes n (%)                               | 3 (9)              | 1 (4)             | 2 (22.2)      |
| Smoke n (%)                                  | 11 (33.3)          | 8 (24)            | 3 (33.3)      |
| Previous Stroke n (%)                        | 7 (21.2)           | 5 (20.8)          | 2 (22.2)      |
| Dyslipidemia n (%)                           | 21 (63.3)          | 15 (62.5)         | 6 (66.6)      |
| Cronin renal failure (CRF) n (%)             | 2 (6)              | 0 (0)             | 2 (22.2)      |
| Atrial Fibrillation n (%)                    | 7 (21.2)           | 6 (25)            | 1 (11.1)      |
| Carotid ATS (moderate or severe at US) n (%) | 16 (48.5)          | 12 (50)           | 4 (44.4)      |

33 patients; 17 Males (51.5%); 16 Females (48.5 %); Mean age 67.6 DS 13.97

Table 2: Times.

| Patients  | Triage-RMN (min) | Wake up-rTpa (min) | RMN-rTpa (min) | Wake up-RMN (min) |
|-----------|------------------|--------------------|----------------|-------------------|
| Patient 1 | 90               | 195                | 67             | 128               |
| Patient 2 | 58               | 280                | 52             | 228               |
| Patient 3 | 56               | 210                | 64             | 146               |
| Patient 4 | 161              | 290                | 69             | 221               |
| Patient 5 | 24               | 160                | 76             | 84                |
| Patient 6 | 82               | 255                | 54             | 201               |
| Patient 7 | 67               | 168                | 61             | 107               |
| Patient 8 | 92               | 200                | 30             | 170               |
| Patient 9 | 30               | 134                | 34             | 100               |

Table 3: Mediantimes.

| Mean time (minutes)  | Triage-RMN    | Wake up-Rtpa  | RMN-rTpa   | Wake up-RMN    |
|----------------------|---------------|---------------|------------|----------------|
| No IVT group (n: 24) | 84.5 (38-165) |               |            | 202 (112-285)  |
| IVT group (n: 9)     | 67 (24-161)   | 200 (134-290) | 61 (30-76) | 146 (84-228)   |
| Total (n: 33)        | 82 (24-168)   | 200 (134-290) | 61 (30-76) | 196.5 (84-285) |

### Conclusion

Although the small sample size, our retrospective analysis seems to confirm the evidence of benefit and safety of reperfusion treatment with alteplase in patients with “wake up stroke” and a MRI finding of an ischemic lesion on DWI but no parenchymal hyperintensity in the same region on FLAIR.

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