

Reperfusion Therapy in Wake-Up Stroke: A Retrospective Observational Study

Abstract

Background and purpose: From all stroke patients, 8% to 27% wake up with symptoms, however they are not eligible for thrombolysis due to the unknown time of onset. Studies have shown that patients with wake-up stroke (WUS) have clinical and radiological characteristics similar to those with known onset time. Thrombolysis and endovascular recanalization seem to improve outcomes in WUS patients.

Hypothesis: thrombolysis with rtPA and/or endovascular therapy was effective and safe in patients with WUS. **Methods:** Retrospective review of acute stroke code database. **Inclusion criteria:** stroke symptoms at awakening and diagnose of acute ischemic stroke.

Exclusion criteria: presence of symptoms before onset of sleep, Last Known Normal-to-needle <270min, previous modified Rankin scale (mRS) ≥ 2 , absolute contraindication for rt-PA and/or endovascular intervention. **Primary outcome:** mRS 0-2 at 90 days. **Secondary outcomes:** NIHSS variation at 24h and at discharge, symptomatic intracerebral haemorrhage, mortality at 90 days.

Results: 29 patients were included in the study. 59% of patients had ASPECTS >7. The most frequent therapeutic intervention was intravenous rt-PA 0.9mg/kg (48.3%; n=14), followed by its association with thrombectomy (24.1%; n=7). Endovascular intervention was done in 91.7% of patients with hyperdense artery sign. Concerning clinical outcomes, NIHSS variation was greater at 24h, symptomatic intracerebral haemorrhage occurred in one patient and the majority of patients had a good functional outcome (75.9%, mRS 0-2 at 90 days).

Conclusion: Thrombolysis seems to be safe in selected wake-up stroke patients. Treated patients have a good functional outcome with low complication risk. A prospective randomized controlled trial is needed to corroborate this data.

Keywords: Acute ischemic stroke; Wake-up stroke; Stroke management; Thrombolysis; Reperfusion therapy; Endovascular therapy; Outcomes

Research Article

Volume 2 Issue 6 - 2015

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Received: June 16, 2014 | **Published:** September 08, 2014

Abbreviations: ASPECTS: Alberta Stroke Program Early CT Score; CT: Computed Tomography; EIC: Early Ischemic Changes; FKA: First Known Abnormal; IQR: Interquartile Range; IV: Intravenous; LKN: Last Known Normal; mRS: modified Rankin Scale; MRI: Magnetic Resonance Imaging; rtPA: recombinant Tissue plasminogen Activator; SD: Standard Deviation; SICH: Symptomatic Intracerebral Haemorrhage; SITS-MOST: Safe Implementation of Thrombolysis in Stroke Monitoring Study; WUS: Wake-Up Stroke

Introduction

Thrombolysis with recombinant tissue plasminogen activator (rtPA) up to 4.5 hours of symptom onset is an established treatment for acute ischemic stroke and improves patient outcome [1-3]. From all stroke patients, 8% to 27% wake up with symptoms, however they are not eligible for thrombolysis due to the unknown time of onset [2,4]. This group of patients has a worse outcome regarding discharge destination and functional outcome [2,5,6]. Moreover, cardiovascular events, as acute myocardial infarction and sudden cardiac death, have a noteworthy circadian variation in the presentation timing. There is an increased risk for both events between 6AM and noon. It

has been proposed that the morning excess of cardiovascular risk is related to the circadian outline of physical activity, blood pressure, plasma catecholamines, and/or plasma cortisol [7-10]. Stroke also has a similar pattern of events. A meta-analysis of 11 816 strokes corroborates evidence that stroke symptoms onset has a circadian variation, with a higher risk in the early morning hours (6 AM to noon), and lower risk during the night time period (midnight to 6 AM). The three stroke subtypes analysed had a considerably higher risk between 6 AM and noon (ischemic strokes: 55%; haemorrhagic strokes: 34%; transient ischemic attacks: 50%) [11]. Interestingly, many patients with wake-up ischemic stroke showed similarities in clinical and radiological characteristics to patients treated with thrombolytic therapy within rt-PA therapeutic window [2,4,12-14]. Studies also suggest that thrombolysis with rtPA or endovascular recanalization may improve outcomes in patients with wake-up stroke (WUS) [15,16]. A 5-fold increase in the likelihood of good functional outcome at 90 days has been shown after adjusting for age, sex and stroke severity, in thrombolysed compared with matched non-thrombolysed WUS patients with no or early ischemic changes on Computed Tomography (CT) imaging [17]. This study hypothesis is that thrombolysis with rtPA and/or

endovascular therapy is effective and safe in patients with WUS.

Materials and Methods

Selection of participants

This was a retrospective, observational study by Stroke Unit Group of São José Hospital in Lisbon. Study subjects were enrolled from consecutive patients admitted to the stroke unit from January 2010 to December 2012. Inclusion criteria were: stroke symptoms at awakening and diagnose of acute ischemic stroke. Exclusion criteria were: presence of symptoms before falling asleep, Last Known Normal-to-needle <270min, previous mRankin score ≥ 2 ; absolute contraindication for rt-PA and/or endovascular intervention. This stroke centre offers thrombolysis to WUS stroke patients with moderate to severe and incapacitating symptoms, based on previous studies that revealed benefit of treatment over no intervention in this group of patients. An informed consent was always provided, by the patient or by a relative as surrogate, prior to therapeutic administration.

Description of participants

Patient characteristics, including sex, age and risk factors were collected from medical records. Cardiovascular risk factors for occurrence of stroke that were recorded are: arterial hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, previous cerebrovascular disease, cardiac failure, current smoking and alcoholism. Recorded timings were Last Known Normal (LKN), First Known Abnormal (FNA), LKN-to-contrast CT, LKN-to-needle, FNA-to-CT, and FNA-to-needle.

Imaging

All patients underwent routine brain-CT imaging and early ischemic changes (EIC) were assessed. As a blinded investigator, a Neuroradiologist with 6 years of experience analysed EIC using Alberta Stroke Program Early CT Score (ASPECTS) of every exam and that score was correlated with the type of treatment selected and with the clinical outcome. Contrast brain-CT imaging was routinely performed. Magnetic Resonance Imaging (MRI) was not routinely performed. When decided by the medical team, MRI was done and mismatch diffusion-FLAIR was evaluated in order to decide most adequate therapeutic approach.

Treatment

Therapeutic options were one of the following: intravenous (IV) rt-PA (0.9mg/kg or 0.6mg/kg), intra-arterial rt-PA, arterial thrombectomy or acute carotid artery stenting if needed.

Since there was no preset protocol, the type of treatment was decided by the treating stroke medical team. All patients were admitted to a specialized stroke unit with a trained medical and nursing team.

Clinical outcomes

Clinical outcomes were defined as primary and secondary. As a primary outcome we defined a modified Rankin scale (mRS) 0-2 at 90 days. As secondary outcomes, NIHSS change at 24h and at discharge, symptomatic intracerebral haemorrhage (SICH) including any intracerebral haemorrhage related to a ≥ 4 point rise in the NIHSS, according to SITS-MOST (Safe Implementation

of Thrombolysis in Stroke Monitoring Study), and mortality at 90 days. This data was collected prospectively from medical records, including the 90 days follow-up visit. In those patients that missed follow-up, a telephone interview was performed to obtain missing data.

Statistical analysis

Data are expressed as mean \pm standard deviation (SD) or median (interquartile range) for quantitative and continuous variables, frequencies and percentages for qualitative or categorical variables. Comparisons were performed using χ^2 test, Fisher exact test, independent samples t test, or Kruskal-Wallis tests as appropriate. Differences at the level of $p \leq 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS (Statistical Package for Social Science-Windows), version 17.

Results and Discussion

Results

During the study period, 35 consecutive WUS patients were identified from our database, however only 29 patients were included in the study. A total of 6 patients were excluded (LKN-to-needle >270min in 4 cases and brain CT showed a cerebral hematoma in 2 patients). The most prevalent risk factors in the study were hypertension, dyslipidemia and tobacco smoking. In respect to the stroke aetiology, according to TOAST classification, the most common was cardioembolism, followed by large artery atherosclerosis (Table 1).

Table 2 describes clinical and imaging/radiologic characteristics. In respect to brain CT, ASPECTS between 8 and 10 was identified in 59% of patients, whereas 34% had a score ≤ 7 . A hyperdense artery sign was present in 41% of cases (Table 2). Brain MRI was performed in 4 patients, and in 3 cases a mismatch DWI-FLAIR was identified.

As it demonstrated in Figure 1, the most frequent therapeutic intervention was intravenous rt-PA 0.9mg/kg ($n=14$), followed by association with thrombectomy ($n=7$), in this case the rt-PA dose administered was either 0.6mg/kg ($n=5$) or 0.9mg/kg ($n=2$). Intra-arterial rt-PA was performed either exclusively or during thrombectomy procedure ($n=2$) (Figure 1).

In Figures 2 & 3 the therapeutic option according to ASPECTS and to the presence of a hyperdense artery sign is displayed. Patients with ASPECTS 8-10 were mainly treated with intravenous rt-PA ($n=11$; 52.4%), while 2 (20%) patients with ASPECTS ≤ 7 were submitted to the same treatment (Figure 2).

With respect to the hyperdense artery sign, 91.7% ($n=11$) of patients were submitted to an endovascular intervention, whereas 76.4% ($n=13$) of patients without hyperdense artery sign were treated with intravenous rt-PA (Figure 3).

Concerning clinical outcomes, a minority of patients developed intracerebral haemorrhage after treatment (only one was considered symptomatic) and the majority of patients had a good functional outcome (75.9%, mRS 0-2 at 90 days). (Table 3, Figure 4). No statistically significant difference was found in functional outcome, regarding LKN-to-needle ($p=0.73$) or FNA-to-needle time ($p=0.99$). The NIHSS variation was greater at first 24h, and only 1 point less at hospital discharge (Figure 5).

Table 1: Baseline characteristics and pathogenesis. TOAST: TrialofOrg 10172 in AcuteStrokeTreatment.

Characteristics	N=29 (%)
Age, mean±SD	66.9 (10.3)
Gender	
o Male	15 (51.7)
o Female	14 (48.3)
Riskfactors	
o Hypertension	19 (65.5)
o Diabetes Mellitus	4 (13.8)
o Dyslipidemia	12 (41.4)
o AtrialFibrillation	3 (10.3)
o Tobacco smoking	9 (31%)
o Alcoholism	2 (6.9)
o Previous cerebrovas cular disease	3 (10.3)
o Cardiacfailure	1 (3.4)
TOAST classification	
o Cardioembolic	10 (34.5)
o Largearteryatherosclerosis	9 (31)
o Smallvessel	3 (10.3)
o Unknown	5 (17.2)
o Other	2 (6.9)

Table 2: Clinical and radiographic characteristics. NIHSS: National Institutes of Health Stroke Scale; IQR: Interquartil Range; LKN: Last Know Normal; CT: Computed Tomography; FKA: First Known Abnormal; ASPECTS: Alberta Stroke Program Early CT score.

NIHSS initial (median(IQR))	15 (21-7)
LastKown Normal (minutes) (mean±SD)	474±150
o LKN-to-CT	485±152
o LKN-to-needle	524±156
FirstKownAbnormal (minutes) (mean±SD)	107±150
o FKA-to-CT	118±45
o FKA-to-needle	157±57
ASPECTS (N (%))	
o 8-10	17 (59)
o ≤7	10 (34)
o undetermined	2 (7)
Hyperdensearterysign (N (%))	12 (41%)

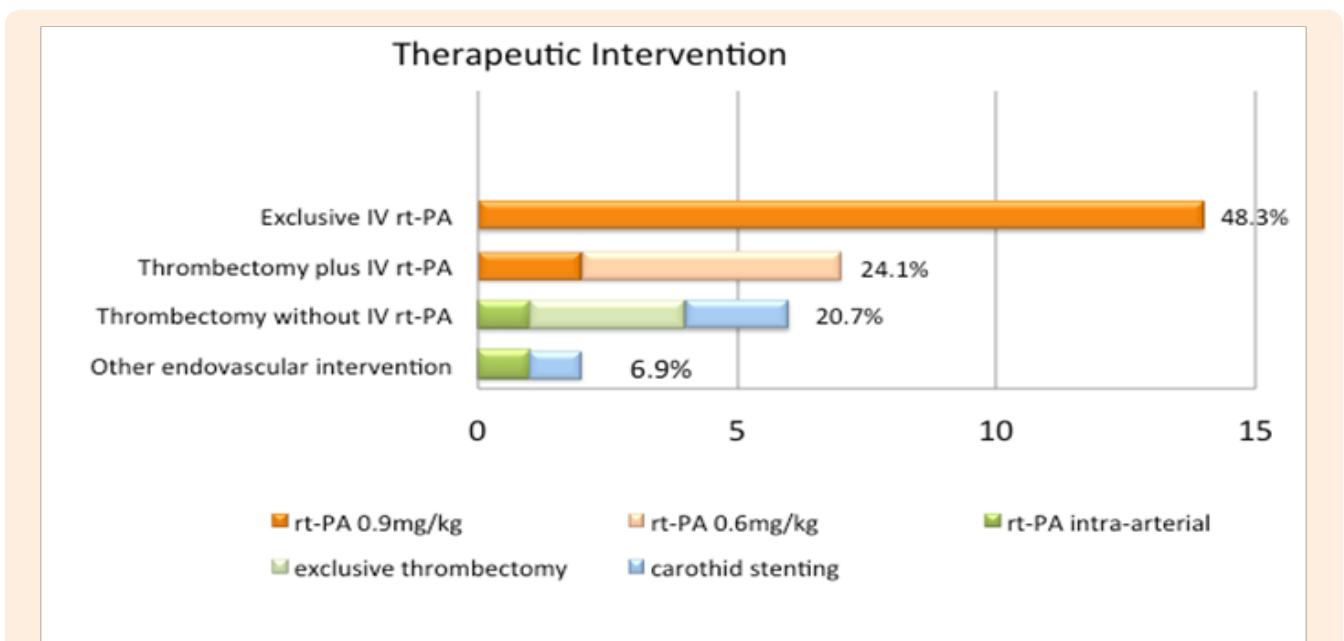


Figure 1: Distribution by type of therapeutic intervention.

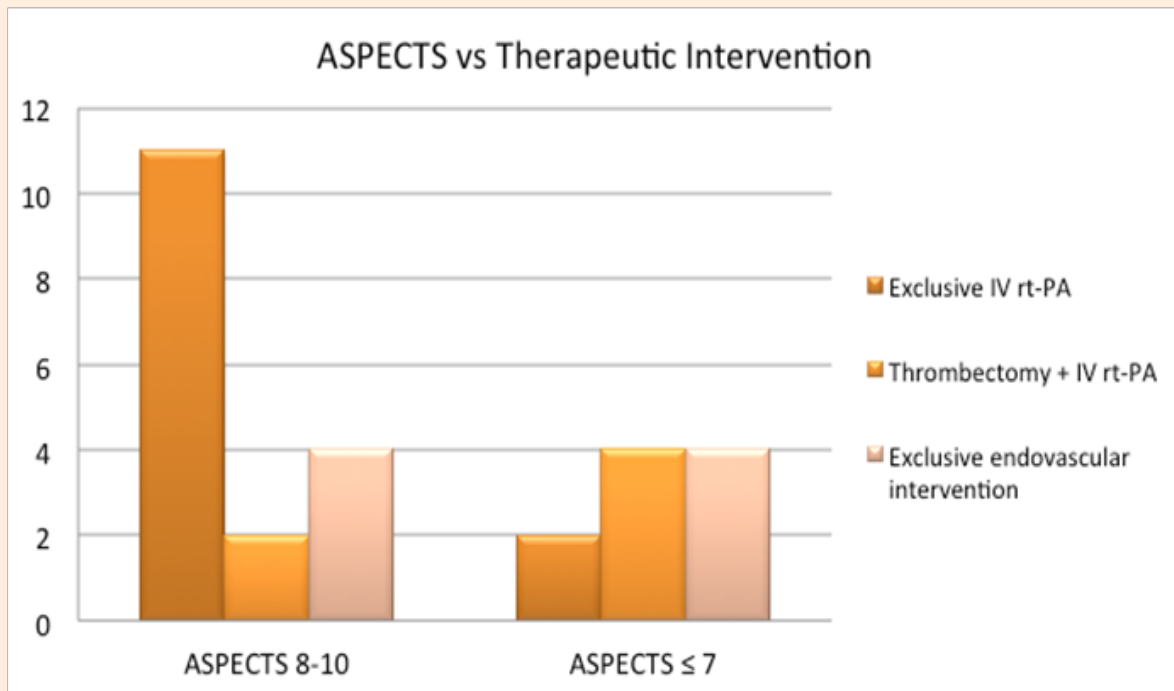


Figure 2: ASPECTS versus Therapeutic Intervention.

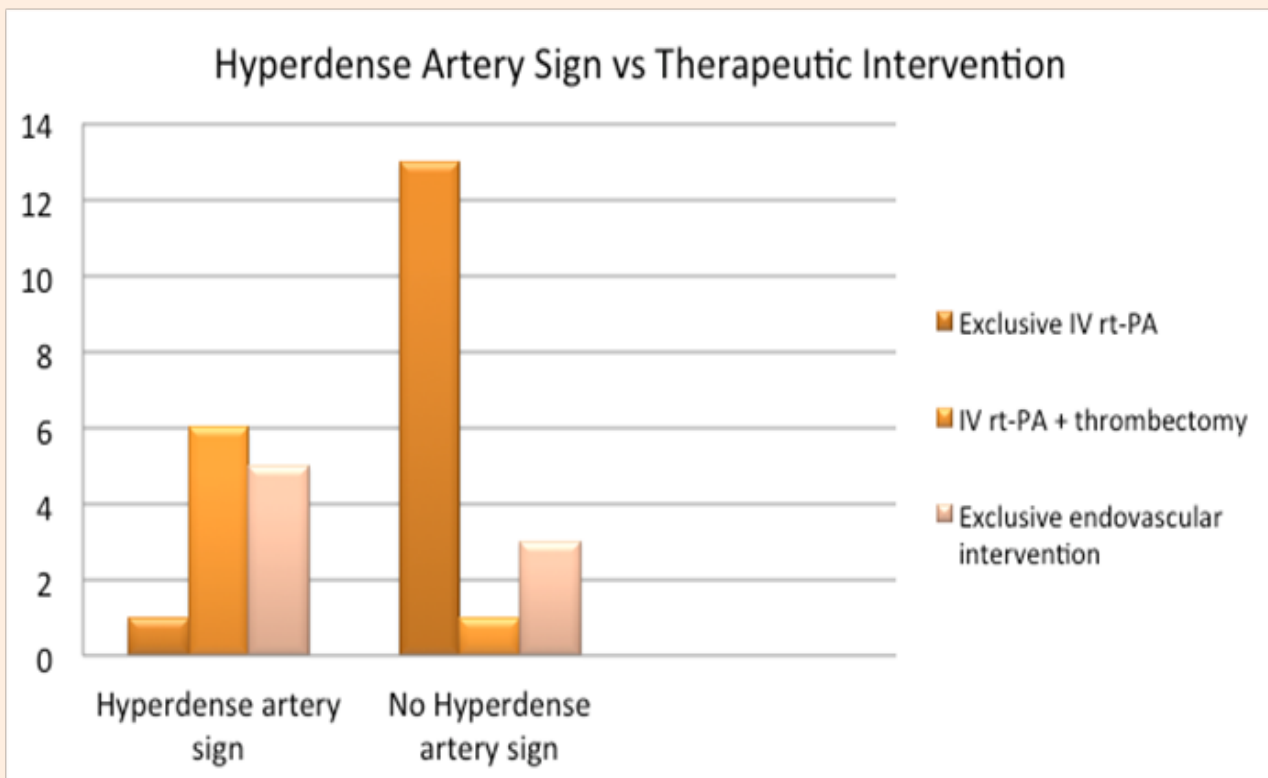


Figure 3: Hyperdense Artery Sign versus Therapeutic Intervention.

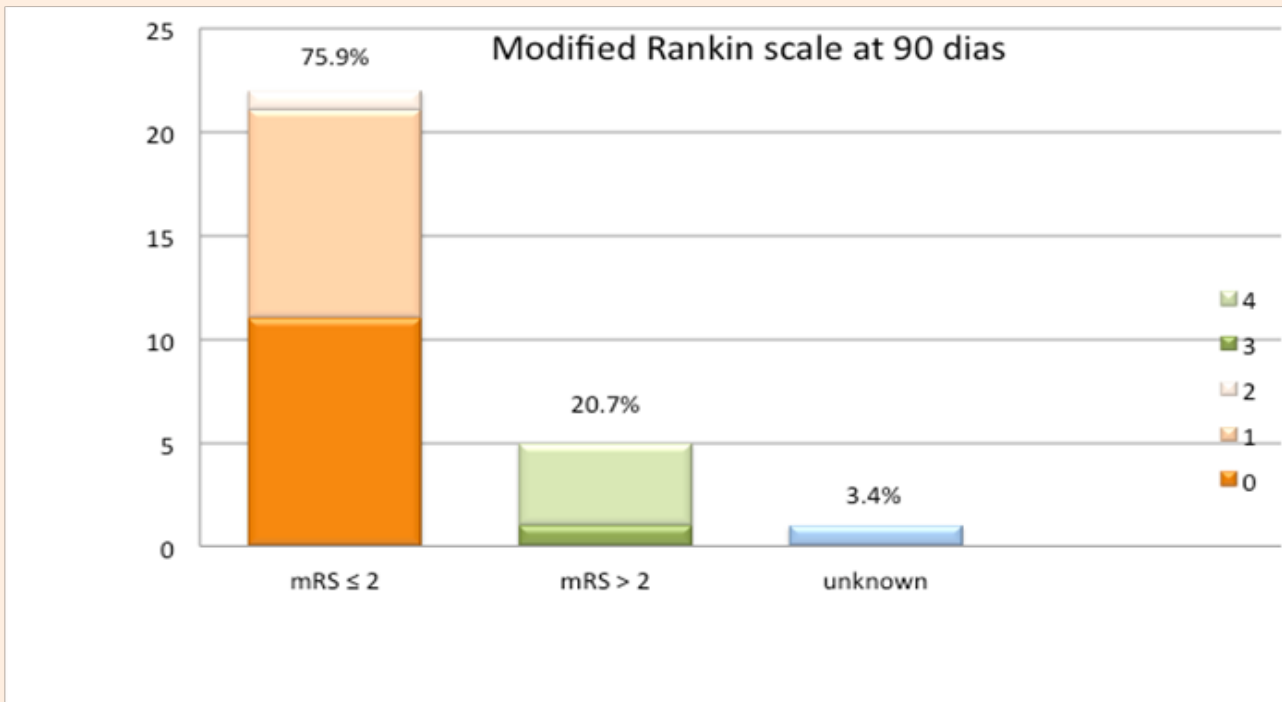


Figure 4: Modified Ranking scale at 90 days.

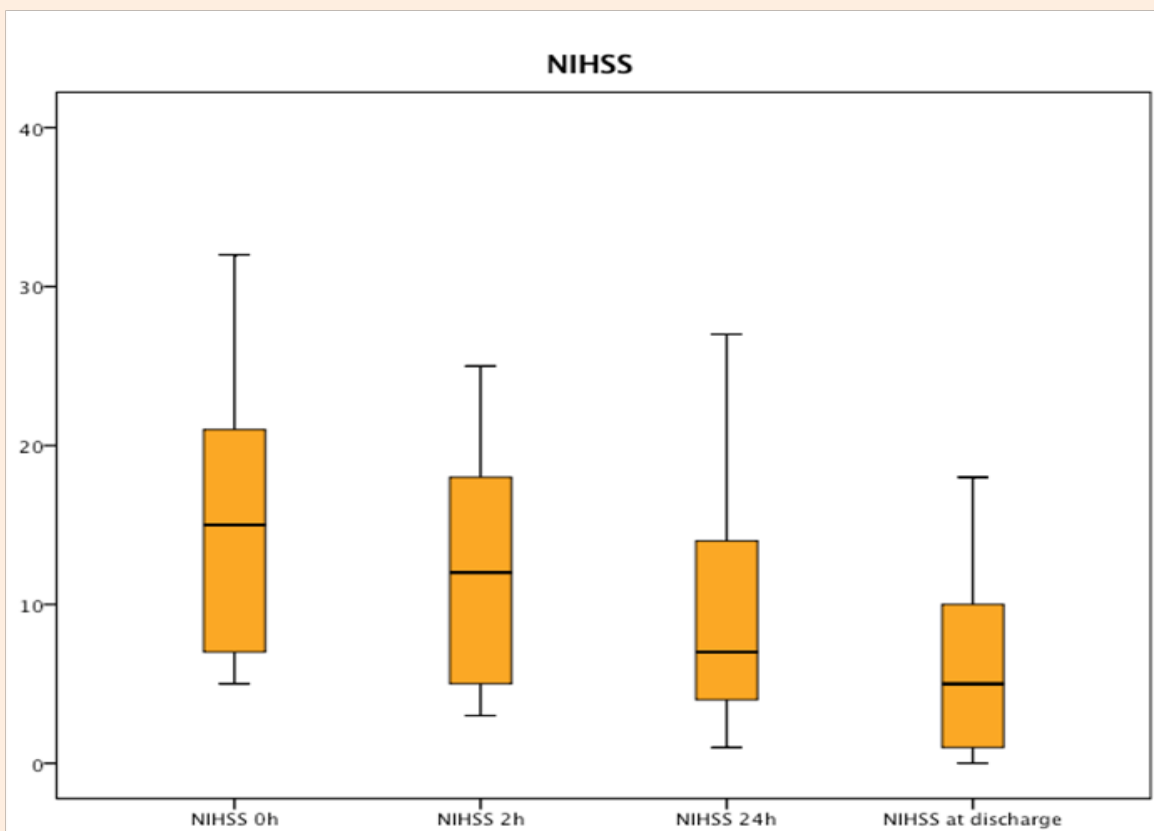


Figure 5: NIHSS evolution.

Table 3: Clinical Outcomes. ICH: Intracerebral Hemorrhage; SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study; NIHSS: National Institutes of Health Stroke Scale; IQR: Interquartile Range; mRankin: Modified Ranking Scale.

Clinical Outcome	n (%)
Intracerebral hemorrhage (ICH)	
o Any ICH	3 (10.3)
o Symptomatic ICH (SITS-MOST)	1 (3.4)
NIHSS (median (IQR))	
o NIHSS 0	15 (21 - 7)
o NIHSS 2h	12 (18 - 5)
o NIHSS 24h	7 (14 - 4)
• Change in NIHSS at 24h	-5 ((-2) - (-11))
o NIHSS at discharge	5 (10.5 - 1)
• Change in NIHSS at discharge	-6 ((-4) - (-14.5))
mRankin	
o mRankin 0 - 2 at 90 days (%)	22 (75.9%)
o mRankin 0 - 1 at 90 days (%)	21 (72.4%)
Mortality at 90 days	0

Discussion

This study details one centre's experience with off-label thrombolysis and thrombectomy in patients with wake-up stroke. Usually WUS patients are not treated with thrombolytic treatment in routine clinical practice because of the uncertainty of symptoms onset. However, as previously described, WUS patients have similar clinical and radiological characteristics to those patients with known time of onset, and therefore may be candidates for treatment [2,4,12-14].

The aetiology in our WUS patients was mainly cardioembolic (34.5%), in contrast to other studies where this aetiology was around 17-19% [18,19]. These differences may be justified by the small sample of this study or due to a higher frequency of atrial fibrillation.

ASPECTS performed in real time are a reliable method for quantification of early ischemic changes [20]. Prior studies found that early ischemic changes on CT from wake-up strokes were similar to acute ischemic stroke patients with known symptoms onset [21-23], ASPECTS dichotomized as >7 and ≤ 7 has been suggested as a predictor of thrombolysis outcome [24].

In our study the majority of the patients had no EIC on CT, defined as ASPECTS 8-10, suggesting a recent stroke onset.

The diffusion and FLAIR mismatch in MRI have been suggested as a better surrogate of time of onset in stroke patients [25]. However, according to medical decision, only 4 patients of our study did MRI and, in fact, 3 of those had mismatch DWI-FLAIR.

The hyperdense artery sign correlates well with the presence of an intra-arterial thrombus. This stroke unit performs routinely endovascular therapy in acute stroke and the majority

of WUS patients in whom an hyperdense artery sign was present has been submitted to thrombectomy (91.7%), either exclusive or after IV rt-PA. On the other hand, in the absence of that sign, the treatment of choice was IV rt-PA.

FKA-to-needle (mean 157min (max 188; min 113)) times were prolonged in our cohort when compared with current guidelines (<60 minutes) [26,27]. This may have happened as a consequence of a slower response of the emergency department and stroke unit team activation, after confirmation of unknown onset time.

WUS is relatively common [2-6,13,21], and thrombolysis may be associated with better outcomes in this group of patients [15-17]. A small randomized controlled trial using CT perfusion selection in 12 patients with unknown time of onset ischemic stroke, showed reperfusion in 4/6 of thrombolysed patients compared with 1/5 in the control group. Several studies showed WUS patients had either excellent or favourable outcomes, when compared to thrombolysed patients within 4.5h of stroke onset [3,28-30]. Manawadu et al. [17] showed that thrombolysis was an independent determinant of a better outcome, with a 5-fold odds of achieving an mRS 0 to 2 at 90 days without increasing the risk of haemorrhage, after adjusting for baseline NIHSS.

In our study 75.9% had a good functional outcome at 90 days, measured by a mRS ≥ 2 .

Two studies reported a frequency of SICH from 2.9% [17] to 4.3% [15], within the range in large registries. In our study, only 1 patient developed SICH (3.4%). The 3 patients that developed an ICH had been submitted to carotid stenting and were under dual anti-aggregation. The patient that developed SICH had an ASPECTS ≤ 7 . All these factors may help explain the increased risk of bleeding.

This study has some limitations. The sample of this study was small and patients were included from one centre only. The small sample may justify a higher number of cardioembolic strokes, and consequently influence the good results. The uncertainty of time onset leads to exclusion of wake-up stroke patients by pre-hospital coordination centre, emergency physicians and triage nurses. In this case, a group of those patients were not included in our acute stroke database. Other limitations are the lack of a systematized imaging algorithm for these patients. At present, in our centre, CT angiography is routinely performed on every acute ischemic stroke patient, to identify major vessel occlusions and for early decision of endovascular treatment. However, in our study, not every patient had a CT angiography. Also, in some centres, routine advanced MR imaging is performed in these cases, allowing a more precise distinction between ischemic and salvageable tissue.

Conclusion

In conclusion, clinical and radiological characteristics seem similar between WUS patients within 4.5h of stroke onset. In this small cohort treated WUS patients had a good functional outcome with few haemorrhagic complications. Thrombolysis appears safe in WUS patients; however randomized controlled trials are needed.

Conflict of Interest

The authors of the submitted article certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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