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Prevalence of early neurological deterioration after I.V – thrombolysis in acute ischaemic stroke patients – A hospital-based cohort study

Christine Krarup Hansen[a,*], Anders Christensen[b], Inger Havsteen[b], Christian Ovesen[a], Hanne Christensen[a]

[a] Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark
[b] Department of Radiology, Bispebjerg Hospital, Copenhagen, Denmark

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ABSTRACT

Objectives: Early Neurological Deterioration (END) occur in up to 25% of patients with ischaemic stroke receiving stroke-unit-care and in 11–13.8% of patients treated with iv-tissue-Plasmniogen-Activator (iv-tPA).

The aim of the study was to establish and compare the prevalence of END and symptomatic Intracranial Hemorrhage (sICH) in a prospectively designed registry of consecutive patients treated with iv-tPA to a historic cohort of iv-tPA eligible patients whom were hospitalized prior to implementation of iv-tPA-treatment but receiving otherwise comparable acute stroke care.

Patients and Methods: Single center registry from a public Danish stroke-unit.

Three-hundred-sixty-one unselected consecutive iv-tPA-treated patients admitted within 4.5 h from symptom-onset with symptoms of acute stroke and > 17 years of age.

The iv-tPA-treated cohort was compared to a pre-tPA cohort of 246 iv-tPA-eligible patients who were admitted to the same stroke center from 1998 to 2001. Acute stroke care apart from iv-tPA was comparable.

Outcome measures was assessed on admission and at 24 h; END as any increase in National Institute of Health Stroke Scale (NIHSS) and symptomatic Intracranial Hemorrhage (sICH) with use of CT-head-scan.

Results: END was observed in 27 (7.5%) of the 361 patients in the tPA-cohort and 43 (17.5%) of 246 in the pre-tPA-cohort, $p < 0.0001$. Any ICH was detected in 23 (6.4%) and sICH in 3 (0.8%) of the iv-tPA-treated patients.

Conclusion: END is significantly less frequent in acute stroke patients treated with iv-tPA. Deterioration due to ICH was rare and of limited severity in this population. END though remains a significant complication after stroke why more detailed knowledge on the various causes of END is needed to further improve patient outcome.

1. Introduction

Early Neurological Deterioration (END) is a well-recognized and feared complication to acute stroke and further predicts poor long-term outcome [1].

Symptomatic Intracranial Hemorrhage (sICH), malignant cerebral oedema, seizures, re-thrombosis, stuttering lacunes, infarct growth, large-artery atherosclerosis and proximal artery occlusions, recurrent stroke, diabetes, older age, coronary heart disease, previous transitory cerebral ischemia, elevated intracranial pressure, leucoaraiosis, infection, fatigue and collateral failure [1–8] have all been described as potential causes of neurological deterioration in patients with acute stroke. Further, a number of biomarkers including glutamate have been suggested to be of importance [9,10]; however, stroke severity has remained the major predictor [10,11].

National Institute of Health Stroke Scale (NIHSS) is presently the most commonly used standardized scale to assess stroke severity [2]. The definition of END has historically been poorly defined, with use of variable stroke scales and levels of deterioration, though a criterion of $\Delta NIHSS \geq 4$ is predominant [1,3].

Prior to implementation of intravenous tissue-Plasminogen-Activator (iv-tPA), END was reported in 9.8–23.7% of patients with symptoms of acute cerebral ischemia [12,13], depending on the definition of END and the type of patients included. Later, END was reported in 5.8–13.8% of iv-tPA-treated patients included in clinical randomized trials and studies of selected patients [1,6,14,15]. sICH is a well-recognised complication to iv-tPA and cause of END. Reported frequencies of sICH varies (1.8–9.5%) between studies [14,16–23]. In the SITS-registry, the frequency of sICH in the same group of patients varied (1.8–7.4%) depending on the definition of sICH applied [23].

* Corresponding author at: Department of Neurology, Bispebjerg Hospital, Neurologisk Forskning og udvikling, Bispebjerg Bakke 23, Opgang 11 A, stuen, 2400 Copenhagen, NV, Denmark.
E-mail address: christinekraruphansen@regionh.dk (C.K. Hansen).

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sICH is however only one mechanism of END and was by Seners et al. reported as the cause of deterioration in only 21.4% of patients with neurological deterioration [1].

The prevalence and cause of END in iv-tPA-treated patients are not well established.

The aim of this study was to report the prevalence of END and sICH in consecutive iv-tPA-treated patients and further to compare the iv-tPA-treated cohort to iv-tPA-eligible patients in a pre-tPA cohort receiving otherwise comparable acute stroke care.

2. Materials and methods

This study is based on two prospective single-hospital cohorts (both from Bispebjerg University Hospital, Denmark):

2.1. The tPA-treated cohort

The tPA-registry included unselected consecutive iv-tPA-treated patients admitted with symptoms of acute cerebral ischemic during a period of 32 months from 2009 to 2011, n = 361. This cohort has previously been described [24–29] including frequencies and location of large vessel occlusions [29]. In short, all patients with symptoms of acute stroke admitted within 4.5 h from onset from a well-defined catchment of the entire Capital Region of Denmark (1.8 million inhabitants) were referred directly by pre-hospital triage. On arrival, clinical status was assessed by NIHSS and a head Computerized Tomography (CT) was conducted prior to administration of iv-tPA.

At 24 h after iv-tPA-treatment, the patients were reassessed by NIHSS and a follow-up head-CT.

To reduce bias, 34 patients treated with endovascular treatment were excluded from this analysis.

2.2. The pre-tPA cohort

The pre-tPA cohort has been described previously [30]. In short, a total of 895 patients with a final diagnosis of ischaemic stroke were admitted within 6 h of symptom onset from a well-defined catchment area comprising Copenhagen and adjacent suburbs from 1998 to 2001. Iv-tPA was at the time not yet implemented in Denmark. Diagnosis of ischaemic stroke was based on clinical findings and CT-scan in all patients. Patients who would have been eligible for iv-tPA (n = 246) (admission < 4.5 h from symptom onset, Scandinavian Stroke Scale Score (SSS) ≤ 56, modified Ranking Scale ≤ 3, no use of anticoagulation therapy and a discharge diagnosis of cerebral ischemic stroke) were included into this analysis. This cohort was assessed with (SSS) on admission and at 24 h after admission. The SSS scores for each patient were converted to NIHSS (NIHSS = 25.68–0.43 *SSS) as described by Gray LJ et al. [31] for comparison to the iv-tPA-treated cohort.

Both cohorts were admitted directly to the same acute stroke unit; providing early swallowing test, mobilization and telemetry within the first 24-h to both cohorts.

The pre-tPA cohort had a CT-scan and was treated with aspirin on admission and vital values were monitored at least every 2 h in the first 24 h of admission.

Iv-tPA-treated patients had continuous monitoring with recordings every 15 min in the first 6 h, then recording of vital values every 2 h.

2.3. CT-methodology

From 1998 to 2001 a Picker single-slice CT-scanner was used and from 2009 to 2011 a 64-section MDCT (Brilliance-64, Philips Healthcare, Best, Netherlands).

Scans were evaluated by two senior neuro-radiological observers who were informed of the presenting symptoms but blinded for all other clinical data.

Presence of ICH was evaluated at 24 h in all iv-tPA-treated patients as any type of ICH as well as according to the ECASS definition; Hemorrhagic Infarction (HI) type I and II, with small petechiae or more confluent patechiae within the infarct respectively, and Parenchymal Hemorrhage (PH) type I and II, with blood occupying less/more than 30% of the infarct with mild/significant space occupying effect respectively [32]. ICH located outside the infarct area was classified as remote ICH and Subarachnoid Hemorrhages (SAH) as presence of blood within the subarachnoid space.

2.4. Outcomes

2.4.1. Neurological deterioration

Patients in both cohorts were stratified as having Early Neurological Deterioration (END) at 24 h of 1–3 or ≥4 Δ NIHSS points compared to admission, calculated as the 24 h-NIHSS-score subtracted the NIHSS admission-score; a negative delta-value thus indicates improvement and a positive value clinical deterioration.

In the iv-tPA-treated cohort, sICH was categorized according to the NINDS, the ECASS and the SITS-MOST definitions to establish generalizability to previous studies. sICH was according to the NINDS criteria defined as; any ICH related to deterioration in the patient's clinical condition [33], and to the ECASS definition as; any ICH combined with a NIHSS increase of ≥4 NIHSS points [23] and SITS-MOST as; a type 2 parenchymal hemorrhage combined with an increase of NIHSS ≥ 4 [23].

2.5. Statistical analysis

Normally distributed continuous data were compared with students-*t*-test and non-parametric distributed continuous data with Mann-Whitney-*U* test/Kruskal Wallis test. Categorical data were expressed as frequencies and compared using Chi-square tests.

NIHSS delta values were calculated as the 24 h score subtracted the admission score.

We designed two logistic regression models to identify predictors of END; one including predictors available on admission and an additional model including the presence of any ICH detected at the 24-h follow-up scan for the iv-tPA treated patients. Due to a low event rate of END, the numbers of predictors possible to test were limited; stroke severity, age and gender were included. ICH present on the 24-h follow up-scan, adjusted for age, gender and time from onset to admission, were separately tested as a predictor of END.

A two-sided P-value < 0.05 were considered significant.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, USA).

The registries were approved by the Danish Data Protection Agency (Files no 2009-41-3824 and 2010-41-5205).

3. Results

Patients' characteristics are presented in Fig. 1 + Table 1. In the tPA-treated cohort, END of any degree was observed in a total of 27 (7.5%) patients; 7 (1.9%) patients had a END of ≥4 NIHSS points (Fig. 1). One patient died within 24 h of treatment due to acute myocardial infarct.

In the pre-tPA cohort, END occurred in 43 (17.5%) of 246 patients (Fig. 1); 21 (8.5%) patients had clinical deterioration of at least 2 NIHSS points and 9 (3.7%) patients of at least 4 NIHSS points at 24 h after admission.

Comparing the two cohorts, the frequency of any degree of END in the iv-tPA-treated patients (7.5%) was significantly lower than in the historic non-treated iv-tPA-eligible cohort (17.5%), p = 0.0001.

When the subgroup of patients with END (Δ1, Δ2, Δ3 and Δ ≥ 4 NIHSS) (Fig. 1) in tPA-treated and pre-tPA cohort were compared respectively, only patients with Δ1 NIHSS in the pre-tPA cohort (8.9%)