neurocritical care society Neurocrit Care (2007) 6:181–185
DOI 10.1007/s12028-007-0018-8

ORIGINAL PAPER

Safety outcomes of Alteplase among acute ischemic stroke patients with special characteristics

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Published online: 13 April 2007

Abstract
Background Although tissue plasminogen activator (tPA) has been approved for use in acute ischemic stroke, concerns linger regarding its safety. We analyzed whether patients in special subgroups (i.e., age >70 years, baseline National Institute of Health Stroke Scale (NIHSS) score >20, diabetes, congestive heart failure (CHF), and of Hispanic origin) have a higher risk of symptomatic intracerebral hemorrhage (SICH) than patients without these characteristics.
Methods Four prospective observational studies of acute ischemic stroke patients treated within 3 h with Alteplase were identified and individual patient data were pooled for this analysis. These included the Standard Treatment with Alteplase to Reverse Stroke Study [STARS, $N = 389$], Epidemiology Study of Ischemic Stroke [ESIS, $N = 236$], University Of Texas Houston Stroke Study [UT, $N = 241$], and Canadian Activase For Stroke Effectiveness Study [CASES, $N = 1100$]. The risk of SICH was calculated for all patients and for each of five subgroups.
Results A total of 1966 patients were studied. Overall the risk of symptomatic ICH was 4.7% (95%CI, 3.8–5.8%) and the risk was similar among patients with and without each of the five characteristics. Patients with advanced age, baseline NIHSS score >20, CHF or diabetes had increased mortality and significantly lower rate of functional recovery.
Conclusions The present study suggests that these specified subgroups of patients are not at increased risk of SICH after stroke thrombolysis compared to those without these characteristics.

Keywords Thrombolysis · Tissue plasminogen activator · Acute ischemic stroke

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Introduction

Despite proven efficacy, concerns remain regarding the safety of tissue plasminogen activator (tPA) for acute ischemic stroke used in routine clinical practice. A recent meta-analysis of 15 open-label studies reported an overall risk of symptomatic intracerebral hemorrhage of 5.2%, lower than the 6.4% rate in the treated group of the randomized, placebo-controlled National Institute of Neurological Disorders and Stroke (NINDS) trial [1, 2]. Risk factors for symptomatic intracerebral hemorrhage (SICH), identified in various studies, include early ischemic changes on the baseline brain CT scan, severity of National Institute of Health Stroke Scale (NIHSS) score, increasing age, congestive heart failure (CHF), baseline systolic blood pressure, baseline glucose level and the use of aspirin before thrombolysis [3–5]. Other concerns include the possibility of ethnic differences in the safety profile. Identification of the risk factors for SICH will help in improved selection of patients for thrombolysis.

We sought to assess the safety profile of stroke thrombolysis among 5 special sub-population known or thought to have a high risk of SICH: (1) those aged > 70 years, (2) severe stroke (NIHSS > 20), (3) diabetics, (4) history of CHF, and (5) Hispanic ethnicity. We estimated the incidence of SICH among patients with acute ischemic stroke treated within 3 h in routine clinical practice and analyzed the safety of tPA in the population with these above characteristics.

Methods

We pooled the data from 4 prospective cohorts of acute ischemic stroke patients treated with intravenous tPA within 3 h of stroke onset in routine clinical practice according to the National Institute of Neurological Disorders and Stroke (NINDS) rtPA protocol. These data included: (1) the Standard Treatment with Alteplase to Reverse Stroke [STARS] study (n = 389); (2) Epidemiological Study of Ischemic Stroke [ESIS] (n = 236); (3) University of Texas Houston Stroke Study [UT] (n = 241); (4) Canadian Activase for Stroke Effectiveness Study [CASES] (n = 1135). A combined total of 94 centers participated in STARS and ESIS, 60 centers in CASES and 4 centers in UT study. All the data were systematically collected (and have been previously reported); any inconsistencies were resolved by contact with the study site personnel. The baseline neurological status was measured using the NIHSS score. No follow-up was available after discharge in the UT study. A 30-day follow-up was available for STARS and ESIS study and 90-day follow-up for the CASES study. The outcome was measured using the modified Rankin score (mRS) and favorable outcome was defined as a score of 0–1. The follow-up CT head was done within 24–36 h in the UT and CASES study and within 72 h in the ESIS and the STARS study. Symptomatic ICH was defined as CT documented hemorrhage associated with decline in the neurological status as judged by the local investigator. Asymptomatic hemorrhage and the CT appearance of the hemorrhage (eg. hemorrhagic infarction or parenchymal hematoma) were not reported. The patients were then categorized into two groups depending on the age > 70 years, NIHSS score >20, presence of diabetes milletus, presence of CHF, and ethnicity (Hispanic origin or not). The risk of SICH and the outcome were assessed and compared between the two groups.

Statistical analysis

Data were pooled from de-identified data sets from each study. Descriptive statistics were used to summarize the data. Proportions with 95% confidence intervals are reported.

Results

The data from the four studies included 1966 patients. The overall SICH rate was 4.7% (95% CI, 3.8–5.9%). The pooled data suggest that the SICH observed in clinical practice is comparable to that observed in NINDS. The number of patients with special characteristics in each of the groups is shown in Fig. 1. There was no statistically significant increase in the SICH rate in any of the five specified subgroups of patients (advanced age, baseline NIHSS > 20, Hispanic ethinicity, diabetes, and CHF). The incidence of combined SICH rate in each of the specified subgroups is shown in Fig. 2.

The 30-day mortality in STARS/ESIS was 13.6% (95% CI, 11.0–16.5%), the 90-day mortality in CASES was 23.3% (95%CI, 20.2–26.5%), and the in-hospital mortality in the UT study was 13.5%(95% CI, 9.3–18.7%). Age > 70 years, baseline NIHSS score >20, history of CHF and diabetes were related to increased mortality in STARS/ESIS and the CASES studies. Favorable outcome data, defined as a mRS score of 0–1, were available only in

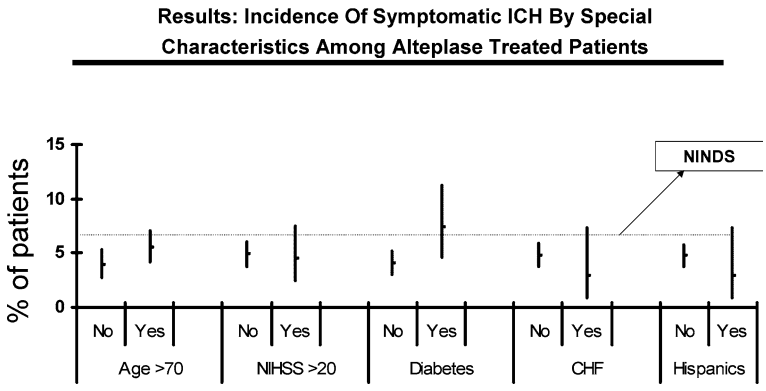

Fig. 1 Proportion of patients with symptomatic hemorrhage by risk group. All groups having overlapping confidence intervals indicating no statistical difference. The comparator rate of 6.4% is shown for the NINDS tPA Stroke Trial

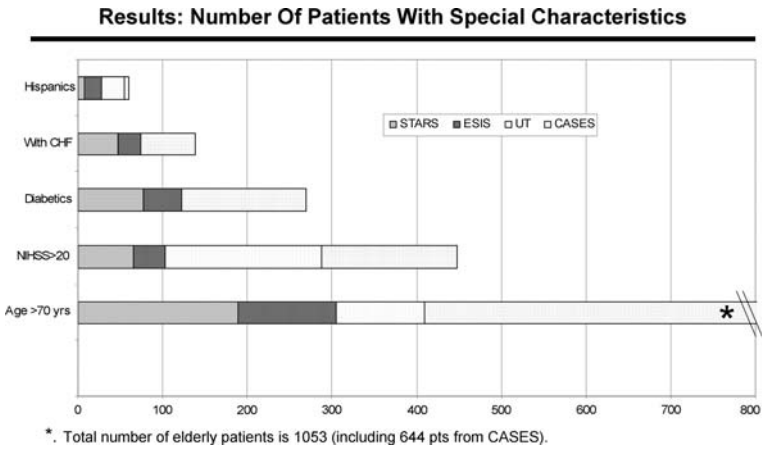

Fig. 2 Results: number of patients with special characteristics. *Total number of elderly patients is 1053 (including 644 pts from cases)

Table 1 Functional recovery (mRS score ≤ 1) by subgroups in the pooled observational Studies [includes STARS, ESIS, and CASES only]

Patient factor [*n*]	Recovery rate (%)	95% CI
Age		
≤70 years [271]	44.7	40.7–48.8
>70 years [178]	25.3	22.1–28.7
Baseline NIHSS score		
≤20 [378]	39.3	36.2–42.5
>20 [32]	14.9	10.4–20.4
History of diabetes		
Yes [61]	27.5	21.7–33.9
No [380]	36.1	33.2–39.1
History of CHF		
Yes [22]	18.6	12.1–26.9
No [415]	36.4	33.6–39.2
Hispanic ethnicity		
Yes [9]	28.1	13.8–46.8
No [441]	34.4	31.8–37.1

CHF = congestive heart failure, NIHSS = National Institute of Health Stroke Scale, mRS = modified Rankin scale

the STARS /ESIS and CASES studies. The combined favorable outcome was 36.3% (95%CI, 33.4–38.7%) which was lower than the rate of functional recovery in patients in NINDS (42.5%; 95%CI, 37.7–48.3%). The patients with advanced age, baseline NIHSS > 20, CHF, and diabetes had a significantly lower rate of functional recovery compared to their counterparts. [Table 1]

Discussion

Our study found that the combined risk of SICH was 4.7%, which was similar to the NINDS study and the risk of SICH in the meta-analysis of the open-label studies. An advantage of pooling individual patient data is that we were able to examine patient subgroups. We found that none of the specified subgroups of patients had a higher risk of SICH (those aged > 70 years, severe stroke (NIHSS > 20), diabetics, history of CHF and Hispanic ethnicity) compared to their counterparts.

In contrast to NINDS tPA Stroke study, we did not find a significant association of severity of neurological deficit at baseline with increased risk of SICH. The first ECASS study has shown that severity of neurological deficit at baseline was a risk factor for hemorrhagic infarction and not for parenchymal hematoma [3]. Similarly, others have noted that stroke severity is not a predictor of symptomatic hemorrhage [6].

Historically, cardioembolic ischemic stroke has been associated with a higher risk of hemorrhagic transformation [7]. But the type of cardiac disease leading on to ICH has been variable among studies, though the final pathophysiological mechanism leading to stroke is the same. Congestive heart failure and atrial fibrillation have both been associated with SICH [5–8]. The present study found that CHF was a not a risk factor for SICH. The disparity among importance of the cause of stroke to hemorrhagic transformation suggests that the effect size, if present, is small. This association needs confirmation from future studies.

Age has been consistently found to be a risk factor for SICH after thrombolysis for both acute ischemic stroke and myocardial infarction [3, 4, 8, 9]. However, we have very little information on the risk of SICH in the elderly from randomized controlled studies to allow us to assess the risk-benefit balance. Recent data from several open-label studies on use of tPA in the elderly have shown that the risk of SICH is comparable to that of their younger counterparts [10–12]. In our study also we found no increased risk of SICH in patients aged more than 70 years. Past cohort studies on the elderly have used a threshold of 80 years to define the high-risk elderly. We have used a cutoff of 70 years, since studies have shown that with advancing age the risk of SICH increases, probably in a continuous

fashion. In a recent study, the rate of SICH increased with age from 4.9% in patients younger than 55 years to 10.3% in patients aged 75 years and older [13]. Approximately half of stroke patients in reported cohorts are over 70 years age, meaning that our choice of threshold, while arbitrary, represents a risk assessment for the oldest half of the population. Nevertheless, it remains prudent to select the elderly patients carefully for thrombolysis.

Elevated baseline blood glucose level has been correlated with ICH risk after thrombolysis [4, 6, 14–16]; a previous study reported that a baseline serum glucose level >11.1 mmol/l was associated with a 25% risk of SICH [14]. The mechanism of hyperglycemia-related ICH is not clear. Hyperglycemia may increase damage to blood brain barrier and enhance the local ischemic injury leading on to an increased risk of SICH. Unfortunately, we did not have complete data on baseline glucose levels. As a surrogate, we did not find that a history of diabetes mellitus was a risk factor of SICH, despite the fact that many patients with diabetes mellitus and stroke present with elevated serum glucose. This may be due to the fact that it is the baseline glucose level, not diabetes mellitus per se, that is predictive of ICH [14].

Several authors have shown ethnic differences in stroke incidence, severity, and mortality [17]. Though the prevalence of hypertension and diabetes is greater among Hispanics compared to non-Hispanics [18], prior data are not available on whether they have at a higher risk of SICH after tPA. This present study showed that the risk of SICH was not higher in Hispanics treated with tPA. Given the importance placed upon ethnic differences in stroke treatment and outcomes by regulatory and funding bodies, these data are reassuring for the treating physician.

One strength of our analysis is that the data were collected from patients treated in the community settings, giving more generalizable information of the risk of SICH in clinical practice. As the patient number was large, a subgroup analysis could be done with sufficient statistical power. Our data were limited by the lack of measurement of early ischemic changes on the baseline brain CT scan and the lack of baseline serum glucose which are important risk factors for SICH [3, 4, 19]. Since the follow-up in each of these studies were not uniform, assessment of the final functional outcome was based upon recorded data. We used the last-score-carried forward principle such that the reported 90-day outcomes included those collected at 30 days or discharge. As usually happens with pooled data sets, the patient populations were not homogenous across studies. Compared to previous studies, we did not find a higher risk of SICH in these high-risk groups. We note that this could be partly due to selection bias as there may have been a tendency to exclude patients from routine treatment who were perceived to be at high risk.

Contributors

SPN wrote the first draft of the article, WD set up the study, did the statistical analysis, helped with data collection, and writing the article, JCG contributed to data collection and writing the article, MKM, KT, and CS helped with data collection, SH contributed to writing the article and MDH contributed to study concept and data collection and writing the article.

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