Safety and Outcome of Thrombolysis in Mild Stroke: A Meta-Analysis

Lei Shi
Min Zhang
Hengfang Liu
Bo Song
Changdong Song
Dandan Song
Yuming Xu

Corresponding Author: Xu Yuming, e-mail: yumingxu@outlook.com
Source of support: Self financing

Background: Whether patients presenting with mild stroke should or should not be treated with intravenous rtPA is still controversial. This systematic review aims to assess the safety and outcome of thrombolysis in these patients.

Material/Methods: We systematically searched PubMed and Cochrane Central Register of Controlled Trials for studies evaluating intravenous rtPA in patients with mild or rapidly improving symptoms except case reports. Excellent outcome (author reported, mainly mRS 0–1), symptomatic intracranial hemorrhage (sICH) and mortality were analyzed.

Results: Fourteen studies were included (n=1906 patients). Of these, 4 studies were comparative (2 randomized and 2 non-randomized). The remaining were single-arm studies. On the basis of 4 comparative studies with a total of 1006 patients, the meta-analysis did not identify a significant difference in the odds of excellent outcome (OR=0.86; 95% CI: 0.64–1.15; I²=0) between IV rtPA-treated minor stroke and those without rtPA treatment. Eleven studies involving 1083 patients showed the pooled rate of excellent outcome was 76.1% (95% CI: 69.8–81.5%, I²=42.5). Seven studies involving 378 patients showed the mortality rate was 4.5% (95% CI: 2.6–7.5%, I²=1.4). Twelve studies involving 831 patients showed the pooled rate of sICH was 2.4% (95% CI: 1.5–3.8, I²=0).

Conclusions: Although efficacy is not clearly established, this study reveals the adverse event rates related to thrombolysis are low in mild stroke. Intravenous rtPA should be considered in these patients until more RCT evidence is available.

MeSH Keywords: Intracranial Thrombosis • Meta-Analysis • Stroke

Abbreviations: sICH – symptomatic intracranial hemorrhage; IV rtPA – intravenous thrombolysis with recombinant tissue plasminogen activator; mRS – Modified Rankin Scale; NIHSS – National Institute of Health Stroke Scale; RCT – randomized controlled trials; IST-3 – The Third International Stroke Trials; ECASS III – European Cooperative Acute Stroke Study

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/892259
Background

Intravenous thrombolysis with recombinant tissue plasminogen activator (IV rtPA) applied within 3 hours or 4.5 hours is efficacious in acute ischemic stroke patients [1–3]. However, few ischemic stroke patients are treated with IV rtPA due to the narrow time window for treatment [4,5]. However, even patients who would generally be eligible are often not treated because of mild stroke or clinical improvement, perceived protocol exclusions, emergency department referral delay, and significant comorbidity [5]. It is very common to not treat patients with mild or rapidly improving symptoms because of an uncertain risk-benefit ratio. In studies evaluating eligibility for thrombolysis, up to 43% of patients with mild or improving stroke symptoms do not receive thrombolytic therapy [6].

However, according to recent reports, 15–31% of patients with mild or rapidly improving symptoms are dependent or dead during hospital admission without thrombolysis [4–7]. In contrast, some researchers have reported that mild stroke patients also benefited from IV thrombolysis, and up to 94% achieved excellent 3-month outcome (modified Rankin Scale, mRS 0–1) [8–10]. At present, no one has truly tested the effectiveness of IV rtPA in mild stroke versus placebo. Studies evaluating intravenous rtPA in mild stroke patients are limited by small sample sizes and non-controlled comparison groups. Until more RCT evidence is available, a systematic review of all studies can provide useful information on the odds for benefits and risks of IV rtPA in patients with mild or rapidly improving symptoms and help decision-making for individual treatment. We therefore conducted this systematic review to assess the safety and outcome of thrombolysis in these patients.

Material and Methods

Search strategy and Eligibility Studies

We systematically searched PubMed (from its earliest date to April 2013), Embase (1980 to May 2013), and Cochrane Central Register of Controlled Trials (The Cochrane library 2013, issue 3) for studies evaluating thrombolysis in patients with mild or rapidly improving symptoms. The terms ‘Minor stroke’, ‘Mild deficit’, ‘Mild symptom’, ‘Mild stroke’, ‘Stroke with rapidly improving symptoms’, ‘Thrombolysis’, ‘Intravenous tissue plasminogen activator’, and ‘rt-PA’ were combined using ‘And’ or ‘Or’ for searching relevant studies. The bibliographies of relevant articles were screened. Studies were included if the following criteria were fulfilled: (1) we considered both comparative (randomized or nonrandomized) and single-arm studies; (2) all patients had been treated for IV rtPA; (3) at least 10 patients were enrolled; (4) at least 1 of following outcomes was expressed as odds ratios (OR) with 95% confidence intervals (CI) and we also obtained the pooled proportions for excellent outcome, mortality, and sICH, including both comparative and single-arm studies. We considered p-values less than 0.05 to be statistically significant.

We evaluated heterogeneity among included studies using the I² test. We considered a value greater than 50% to indicate substantial heterogeneity. Regardless of the size of heterogeneity, a random effects model was used for statistical analysis. We conducted the meta-analysis using Cochrane RevMan 5.1 software and Meta-analyst (version 3.13beta; Tufts Medical Center) [11].

Results

Studies identified

The selection of studies is depicted in Figure 1. The initial literature search identified 461 relevant articles. After reading titles and abstracts, we retained 32 studies for further assessment; of these, we excluded 20 studies [12–31]. Two additional studies were included by reference list screening. Ultimately, 14 studies, containing 1906 patients, were included in this systematic review [8–10,32–42]. Two studies were subgroup analyses from previous RCTs (NINDS 1995 and IST-3) [9,37]. The remaining studies were observational studies (single-arm), of which 2 studies had a concurrent control group. Thus, 4 studies (2 randomized and 2 nonrandomized) contributed data to both the rtPA group and the non-rtPA group. The number of participants ranged from 19 to 535 (Table 1).
Figure 1. Flow chart of literature screening and selection process.

Characteristics of included studies

The mean age of participants ranged from 59 to 70 years. The proportion of male participants was 55.6-78.9% among these trials. Most of studies enrolled patients treated within 3 hours. All studies except 1 used NIHSS as criteria for mild stroke. Usual cut-off to define mild stroke was NIHSS 4, 5, or 6. More details are given in Tables 1 and 2.

Outcome rates

Four comparative studies evaluated the effect of IV rtPA on excellent outcome. On the basis of these studies with a total of 1006 patients, the meta-analysis did not identify a significant difference in the odds of excellent outcome (OR=0.86; 95% CI: 0.64–1.15; I²=0) between IV rtPA-treated minor stroke and those without rtPA treatment (Figure 2).

We also calculated the pooled proportions for excellent outcome, mortality, and sICH, including both comparative and single-arm studies in patients with mild stroke receiving IV rtPA. The excellent outcome was available for 11 studies (1083 patients). It was reported to range from 57.6% to 100%. The pooled proportion of excellent outcome was 76.1% (95% CI: 69.8–81.5%, I²=42.5) (Figure 3). Seven studies involving 378 patients showed the risk of mortality rate ranged from 0% to 8%, with a pooled 90-day mortality rate of 4.5% (95% CI: 2.6–7.5%, I²=1.4) (Figure 4). Regarding the definition of sICH, 4 studies defined it as clinical neurological deterioration temporarily related to ICH [9,10,33,36] and 2 defined it as a ≥4-point increase in NIHSS associated with ICH [8,38]; 1 defined clinical neurological deterioration or a ≥4-point increase in NIHSS associated with ICH [41]; the definition was unclear in the remaining studies [32,34,35,40]. The risk of sICH was reported to range from 0% to 5.1%. Twelve studies involving 831 patients showed the pooled rate of sICH was 2.4% (95% CI: 1.5–3.8, I²=0) (Figure 5).

Discussion

Thrombolysis is often withheld in patients with mild symptoms, so little is known about its efficacy and safety in these patients. Our study suggests that there are no significant differences for excellent outcome after 3 months of IV rtPA-treated minor stroke compared with those without rtPA treatment. The pooled estimates associated with IV rtPA were 76.1% for excellent outcome, 4.5% for mortality rate, and 2.4% for sICH.

In previous studies, the proportion of poor outcome (mRS 2-6) in mild patients who do not receive IV rtPA varied from 15% to 31%. Our study showed the pooled proportion of excellent outcome (mRS 0-1) was 76.1% for mild patients receiving IV rtPA, which is similar to the results mentioned above. A post hoc subgroup analysis of the NINDS study with small group of patients suggested that the risk-to-benefit ratio for using t-PA in patients with minor stroke favored treatment in eligible patients [9]. However, the subgroup analysis of the IST-3 trial did not show a significant effect of rt-PA in patients with mild stroke [37]. This may be due to the treatment effect being
Table 1. Characteristics and outcome of studies on minor stroke treated with intravenous tissue plasminogen activator.

| Study          | Study type                  | N  | Definition | Time  | Age    | Male,% | NIHSS | Functional outcome | sICH | Mortality 90 |
|----------------|-----------------------------|----|------------|-------|--------|--------|-------|-------------------|------|--------------|
| **Comparative studies** |                             |    |            |       |        |        |       |                   |      |              |
| Khatri, 2010  | RCT post hoc analysis       | 42 | NIHSS ≤5   | 3 hours | NG    | NG    | NG    | mRS 0–1           | 1/42, 2.4% | NG           |
| Sandercock, 2012 | RCT post hoc analysis       | 304 | NIHSS ≤5   | 6 hours | NG    | NG    | NG    | OHS 0–2           | NG   |              |
| Huisa, 2012   | Prospective Stroke registry | 59 | NIHSS ≤5   | 3 hours | 66.5  | (16.4)| 61%   | mRS 0–1           | 3/5, 5.1% | NG           |
| Urrea, 2013   | Prospective Stroke registry | 119 | NIHSS ≤5  | 4.5 hours | 68.8  | (13.8)| 69%   | Median 3 (2–4)     | 2/119, 1.7% |              |
| **Single arm studies** |                             |    |            |       |        |        |       |                   |      |              |
| Steffenhagen, 2009 | Prospective Stroke registry | 77 | NIHSS ≤5   | 3 hours | 65    | (12) | 48%   | mRS 0–1           | 2.6%, 2/77 | 6/77, 8%   |
| Strbian, 2012 | Prospective thrombolysis registry | 194 | NIHSS 3–4 | 3 hours | 62    | (58–73)| 116/194, 59.8% | 0 (0–2) | 45/58, 77.6% | 5, 2.6% |              |
| Kohrmann, 2009 | Prospective Stroke registry | 32 | NIHSS≤5    | 2 (1–12)| 69.5  | (42–92)| 30/58, 51.7% | 116/194, 59.8% | 0       |              |
| Baumann, 2006 | Prospective thrombolysis registry | 19 | RIE*       | 3 hours | 59    | (13)  | 15/19, 78.9% | 15/19, 78.9% | 0       | 1/19, 5.3%    |
| Nesi, 2014    | Prospective Stroke registry | 47 | NIHSS ≤6   | 3 hours | NG    | NG    | NG    | mRS 0–1           | 41/47, 87.2% | 0           |
| Joshua Z, 2011 | Prospective database        | 535 | NIHSS ≤5  | 3 hours | NG    | NG    | NG    | NG                | Mortality discharge | 10/535, 1.9% |
| Mittal, 2012  | Stroke Center database      | 25 | NIHSS ≤5   | 3 hours | 66.5  | (12.5)| NG    | NG                | 1/25, 4% | Death/ Hospice (discharge) | 2/25, 8% |
| Desilles 2011 | Prospective database        | 25 | NIHSS ≤4   | 4 (0–4) | NG    | NG    | NG    | mRS 0–2           | 0       | 0            |
| Hassan, 2010* | Retrospective study         | 27 | NIHSS ≤6   | 3 hours | 62.4  | (14.3)| 15/27, 55.6% | Mean 4.52 (1.25) | 1/27, 3.7% | NG           |
| Wendt, 2013   | Hospital thrombolysis database | 107 | NIHSS ≤4  | 71 (64–78)| 66/107, 62% | 36/65, 55% | NG   | mRS 0–1           | 1/107, 0.9% | NG           |

* RIE: Rapid early improvement of neurological deficit (defined as regression of neurological symptoms between stroke onset and evaluation by the treating neurologist); ** 7–10 days or discharge; OHS – Oxford Handicap Score; RCT – randomised controlled trial; NIHSS – National Institutes of Health Stroke Scale; mRS – modified Rankin Scale; sICH – symptomatic Intracranial Hemorrhage; NG – not given.
too small to be detected, and would require a very large sample. A second reason why IST may not have shown a benefit of rt-PA in mild strokes is because the treatment window was 6 hours and this was a criterion for inclusion into the trial.

The main reason of the exclusion from thrombolysis in patients with mild symptoms is the fear that rtPA will present a potential risk for cerebral hemorrhage. Our results demonstrated that the rate of sICH in IV rt-PA treated patients with mild stroke (2.4%) was similar to the rate of hemorrhage in the control group (1.8%) from a recently updated meta-analysis of rtPA for acute ischemic stroke (12 trials, 7012 patients) and lower than in treated patients (7.7%) [43]. It is also lower than the result of SITS-MOST containing 6483 treated patients with minor stroke [44].

**Table 2.** Subgroup analyses of outcomes according to different time and NIHSS.

| Subgroup | Number of study and participants | Excellent outcome OR 95%CI | Number of study and participants | Mortality OR 95%CI | Number of study and participants | sICH OR 95%CI |
|----------|---------------------------------|---------------------------|---------------------------------|-------------------|---------------------------------|----------------|
| **Time** |                                 |                           |                                 |                   |                                 |                |
| ≤3 hours | 6,496                           | 0.727 (0.634–0.805)       | 202                            | 0.060 (0.033–0.107) | 548                            | 0.028 (0.016–0.046) |
| ≤6 hours | 1,304                           | 0.727 (0.674–0.774)       | –                              | –                 | –                              | –              |
| **NIHSS**|                                 |                           |                                 |                   |                                 |                |
| ≤3       | 1,65                            | 0.738 (0.619–0.831)       | –                              | –                 | 1,65                            | 0.015 (0.002–0.101) |
| ≤4       | 4,416                           | 0.891 (0.519–0.984)       | 2,57                           | 0.017 (0.002–0.111) | 4,416                           | 0.017 (0.008–0.036) |
| ≤5       | 5,601                           | 0.740 (0.659–0.808)       | 3,255                          | 0.047 (0.020–0.105) | 5,322                           | 0.032 (0.015–0.063) |
| ≤6       | 2,535                           | 0.750 (0.401–0.930)       | 1,47                           | 0.01 (0.001–0.146)  | 2,76                            | 0.037 (0.005–0.221) |

NIHSS – National Institutes of Health Stroke Scale; sICH – symptomatic intracranial hemorrhage.

**Figure 2.** Odds ratio for ‘Excellent outcome’ after 3 months of intravenous rtPA-treated minor stroke compared with those without rtPA treatment.
Figure 3. Pooled proportion of excellent outcome at the end of 3 months.

| Study name     | N   | Rate: 95% CI               |
|----------------|-----|----------------------------|
| Khatri (2010)  | 42  | 0.786 (0.637, 0.885)       |
| Sandercock (2012)| 304 | 0.727 (0.674, 0.774)       |
| Huisa (2012)   | 59  | 0.576 (0.448, 0.695)       |
| Urra (2013)    | 119 | 0.832 (0.754, 0.889)       |
| Steffenhagen (2009)| 77 | 0.753 (0.645, 0.837)       |
| Strbian (2012) | 252 | 0.639 (0.576, 0.696)       |
| Kohrmann (2009) | 32  | 0.938 (0.782, 0.984)       |
| Baumann (2006) | 19  | 0.789 (0.554, 0.919)       |
| Nesi (2013)    | 47  | 0.872 (0.744, 0.942)       |
| Desilles (2011)| 25  | 1.000 (0.756, 1.000)       |
| Wendt (2013)   | 107 | 0.738 (0.647, 0.813)       |
| Overall        |     | 0.761 (0.698, 0.815)       |

Figure 4. Pooled mortality at the end of 3 months.

| Study name     | N   | Rate: 95% CI               |
|----------------|-----|----------------------------|
| Huisa (2012)   | 59  | 0.051 (0.016, 0.146)       |
| Urra (2013)    | 119 | 0.017 (0.004, 0.065)       |
| Steffenhagen (2009) | 77 | 0.078 (0.035, 0.163)       |
| Kohrmann (2009) | 32  | 0.000 (0.000, 0.201)       |
| Baumann (2006) | 19  | 0.053 (0.007, 0.294)       |
| Nesi (2013)    | 47  | 0.000 (0.000, 0.146)       |
| Desilles (2011)| 25  | 0.000 (0.000, 0.244)       |
| Overall        |     | 0.045 (0.026, 0.075)       |

Figure 5. Pooled rate of symptomatic intracranial hemorrhage.
patients, which assessed the safety profile of Alteplase in clinical practice [44].

The main limitation of this study is that most of the included studies that described the outcome either used historical controls or no control group and the patient count was low. A further limitation in this combined analysis is lack of adjustment on baseline differences. In addition, there is no consensus definition of minor stroke. The NINDS t-PA study and the ECASS III [1,2] both excluded patients with mild stroke, but they failed to clearly define a threshold for mild stroke. So far, although there are no identical variants for predicting the poor outcome of patients with minor stroke, future studies are needed to focus on how to really identify minor stroke patients with poor outcome by clinical features combined with imaging features. Previous studies found that mild stroke patients with large-vessel occlusion were at high risk for early neurological deterioration or poor outcome [45]. Imaging with advanced MRI is a possibility to guide treatment decision-making in mild stroke [27,34,36]. However, the decision-making process regarding these techniques seems to be rather sophisticated. These issues should be addressed in further randomized controlled clinical trials.

Conclusions

Although efficacy is not clearly established, this study reveals that the adverse event rates related to thrombolysis are low in mild stroke. Intravenous rPA should be considered in these patients until more RCT evidence is available.

Competing interests

The authors declare that they have no competing interests.

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