Thrombolysis for Acute Ischemic Stroke

Joanna M. Wardlaw, MB ChB, FRCR, FRCP, FMedSci; Veronica Murray, MD, PhD; Eivind Berge, MD, PhD; Gregory J. del Zoppo, MD

Background
Recombinant tissue plasminogen activator (rtPA) is licensed for thrombolytic therapy in ischemic stroke if administered within 3 hours of stroke onset in selected patients (to be extended to 4.5 hours in some countries). However, many patients who could benefit from rtPA are not offered it and there is evidence that rtPA could benefit many patients who do not meet current license criteria. Furthermore, the patient characteristics that might assist in stratifying risk and benefit and the latest time at which thrombolysis may be effective remain unknown.

Objectives
The objectives of this study were to assess the safety and efficacy of thrombolytic agents used in acute treatment of ischemic stroke, factors that might influence risk or benefit, and estimate if current data can identify the latest time window for treatment.

Search Methods
We used the Cochrane Stroke Group Trials Register, MEDLINE, and EMBASE; contact with trialists, and hand-searching of pertinent journals (all to October 2008).

Selection Criteria
Selection criteria were randomized trials of any thrombolytic agent compared with a control in patients with definite ischemic stroke.

Data Collection and Analysis
Two reviewers applied the inclusion criteria, extracted the data (published and unpublished), and assessed trial quality. We calculated ORs and 95% CIs for all main outcomes using fixed effects methods (additionally by random effects methods where significant between-trial heterogeneity was present), calculated the effect per 1000 patients treated, and performed sensitivity analyses on key variables.

Main Results
Twenty-six trials with data on 7152 patients testing urokinase, streptokinase, rtPA, recombinant prourokinase, or desmoteplase were included. Fifty-six percent of all data came from trials testing rtPA (11 trials, 3977 patients). Four trials used intra-arterial administration (all non-rtPA); the rest used intravenous treatment. Most data come from trials that started treatment up to 6 hours after stroke onset. Among more recent trials, 3 treated up to 9 and 1 up to 24 hours after stroke onset. Twenty-three trials used plain CT scanning for brain imaging, 3 trials used a version of the “mismatch concept” to include/exclude patients, and 1 further trial collected data on mismatch. Very few patients (0.5% of all data, approximately 1% of rtPA data) were aged >80 years. There were imbalances in key prognostic variables and several did not have complete blinding of outcome assessment. The results for all thrombolytic drugs were similar, but we focus on rtPA data (Table).

Among trials testing recombinant tissue plasminogen activator (rtPA), there was a significant increase in symptomatic and fatal intracranial hemorrhage (ICH) and a nonsignificant increase in total early and late deaths (ie, within the first 7 to 10 days and by 3 months, respectively; Table). Fatal ICH accounted for most of the nonsignificant excess of total early deaths, because removing the fatal ICH from the total early deaths showed that rtPA significantly reduced the odds of early death from non-ICH causes. Furthermore, among patients who survived the first 7 to 10 days, there was no subsequent excess of deaths with rtPA (Table).

rtPA significantly reduced the proportion of patients with modified Rankin Scale (mRS) score 3 to 6 at 3 months after stroke (Table). In absolute numbers, for every 1000 patients treated during the first 6 hours after stroke, 60 (95% CI, 30 to 90) fewer patients were dead or dependent at late follow-up. However, there was significant heterogeneity of treatment effect (all drugs, $I^2$ 38%, $P=0.04$; rtPA trials, $I^2$ 62%, $P=0.007$). A random effects analysis produced slightly less
Table. Summary of the Effects of rtPA on Main Outcomes From 11 Trials Including 3977 Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events within 7–10 days: treatment up to 6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths within 7–10 days</td>
<td>1.23 (0.88, 1.71)</td>
<td>0.43</td>
<td>0% (0.43)</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>3.70 (2.36, 5.79)</td>
<td>&lt;0.00001</td>
<td>0% (0.46)</td>
</tr>
<tr>
<td>Death not due to ICH</td>
<td>0.63 (0.41, 0.98)</td>
<td>0.04</td>
<td>0% (0.68)</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3.28 (2.48, 4.33)</td>
<td>&lt;0.0001</td>
<td>24% (0.22)</td>
</tr>
<tr>
<td>Major infarct swelling</td>
<td>0.79 (0.62, 1.01)</td>
<td>0.06</td>
<td>34% (0.18)</td>
</tr>
<tr>
<td>Events by 3 months; treatment up to 6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths by 3 months</td>
<td>1.14 (0.95, 1.38)</td>
<td>0.16</td>
<td>40% (0.08)</td>
</tr>
<tr>
<td>Deaths between 10 days and 3 months</td>
<td>1.04 (0.75, 1.45)</td>
<td>0.82</td>
<td>0% (0.60)</td>
</tr>
<tr>
<td>Death or dependency (mRS 3–6)</td>
<td>0.78 (0.68, 0.88)</td>
<td>0.0001</td>
<td>62% (0.007)</td>
</tr>
<tr>
<td>Death or dependency (mRS 2–6)*</td>
<td>0.76 (0.66, 0.87)</td>
<td>0.0001</td>
<td>66% (0.003)</td>
</tr>
<tr>
<td>Death or dependency (mRS 3–6)*</td>
<td>0.79 (0.69, 0.90)</td>
<td>0.0004</td>
<td>42% (0.09)</td>
</tr>
<tr>
<td>Dependency (mRS 3–5)</td>
<td>0.71 (0.62, 0.81)</td>
<td>&lt;0.0001</td>
<td>31% (0.17)</td>
</tr>
<tr>
<td>Events by 3 months; treatment &lt;3 hours versus 3–6 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead or dependent (mRS 3–6) treatment &lt;3 hours†</td>
<td>0.64 (0.50, 0.83)</td>
<td>0.0008</td>
<td>0% (0.77)</td>
</tr>
<tr>
<td>Dead or dependent (mRS 3–6) treatment 3–6 hours†</td>
<td>0.85 (0.73, 0.99)</td>
<td>0.04</td>
<td>34% (0.18)</td>
</tr>
</tbody>
</table>

*Only trials that provided data for both mRS 2–6 and 3–6 are included in this analysis.
†Only trials that randomized patients in both time windows are included in this analysis.
I² indicates a measure of heterogeneity; the larger the I², the greater the heterogeneity in outcome between studies.

positive, although still statistically significant, results. Among survivors (mRS score 3 to 5), rtPA significantly reduced dependency with no heterogeneity (Table).

Defining “poor outcome” at 3 months as mRS score 2 to 6 gave a more positive effect on functional outcome than for mRS score 3 to 6 that did not reach significance (note this analysis is restricted to just those trials that provided both outcomes; Table). However, using mRS score of 2 to 6 was associated with significant heterogeneity, whereas mRS score of 3 to 6 was not, indicating that mRS score of 3 to 6 may provide not just a more cautious, but also a more robust estimate of rtPA effect.

Several factors could modify the effect of thrombolysis and explain the heterogeneity. These indirect comparisons should be treated with caution and regarded as hypothesis-generating rather than reliable evidence (note full details in Wardlaw et al†). For example, rtPA given within 4 hours of stroke appeared more effective in reducing death or dependency, but there was still benefit between 3 and 6 hours (Table). Patients with moderate stroke (National Institutes of Health Stroke Scale score approximately 10 to 15) may get most benefit from thrombolysis and patients with severe stroke (National Institute of Neurological Diseases and Stroke score approximately 18 to 30) the least benefit, but these analyses are based on small samples. Data were insufficient to examine the effect of visible infarct signs on CT. Results of studies selecting patients using MR diffusion/perfusion imaging mismatch were similar to results of studies that selected patients on the basis of plain CT, although direct comparisons were difficult because there were other differences than imaging between the studies.

Authors’ Conclusions

Overall, among the selected populations of patients included in the trials to date (99% of whom were aged <80 years), rtPA significantly reduced the proportion of patients with poor outcomes after stroke (and conversely increased the proportion of patients with good outcomes). This overall benefit was apparent despite a nonsignificant increase in deaths, mostly attributable to ICH. There were insufficient data to determine the risk–benefit ratio for different categories of patients.

Applicability of Findings to Clinical Practice

Use of rtPA within the existing license is supported by the available evidence, but data are insufficient to determine risks and benefits in clinically important subgroups of patients, especially those aged >80 years, but also by vascular risk factors and medical history, brain scan appearances, stroke subtype, or the latest time for benefit.

Future Research

More data are required to determine the magnitude of overall benefit in clinically important subgroups of patients, especially those aged >80 years, but also by time to treatment; grades of stroke severity; subtypes of stroke (eg, lacunar, cortical); comorbidities such as diabetes, hypertension, and prior stroke; aspirin use before stroke; and findings on different kinds of brain imaging. To answer these questions reliably, and in particular to be able to tailor treatment to the individual and increasingly more complex patient with stroke, more data are needed from new randomized controlled trials.

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Disclosures

None.

Reference


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急性缺血性卒中的溶栓治疗
Thrombolysis for Acute Ischemic Stroke

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(Stroke. 2010;41;e445-e446. 张灿飞 译 曾进胜 校)

背景
重组组织型纤溶酶原激活物 (rtPA) 被准许用于发病 3 小时内的缺血性卒中患者 (适时的患者，在某些国家可放宽到 4.5 个小时) 的溶栓治疗。然而许多能够从 rtPA 中获益的患者并未能接受 rtPA 治疗，并且有证据表明 rtPA 能够使不符合现行纳入标准的患者受益。然而，哪些患者特征有助于风险 / 获益分层和治疗时间窗的判断目前仍然不清楚。

目的
本研究的目的是评估溶栓剂急诊治疗缺血性卒中的安全性和有效性以及影响风险或获益的因素，并评估目前的数据能否确定最晚的治疗时间窗。

检索方法
我们检索了 Cochrane 卒中组的注册试验、MEDLINE 以及 EMBASE 数据库，联系试验者，并手工检索了相关文献 (截止到 2008 年 10 月)。

纳入标准
纳入标准是：对确诊的缺血性卒中患者，采用任何一种溶栓剂与对照物比较的随机试验。

数据收集和分析
两个评价者依照纳入标准提取资料 (已出版和未出版)，评估试验的质量。我们用固定效应模型，计算出所有主要结局的比值比 (ORs) 和 95% 可信区间 (CI)(试验间的异质性明显时用随机效应模型)，计算平均治疗每 1000 名患者的有效性，并对主要变量做敏感性分析。

主要结果
26 个试验包括 7152 名患者，这些研究使用了尿激酶、链激酶、rtPA、重组人尿激酶原或者去氨普酶。所有资料中 56% 来自于 rtPA 的试验 (11 个试验，3977 名患者)。4 个试验采用动脉内溶栓 (全都不是 rtPA)，其余全部采用静脉内溶栓。大多数据来自于卒中发生后长达 6 个小时内的溶栓。在最近的试验中，3 项研究在卒中后长达 9 个小时内溶栓，1 项研究在卒中发生后的 24 小时内溶栓。23 项研究用普通 CT 扫描脑成像，3 项研究用“不匹配概念”来排除或纳入患者，其中 1 项进一步收集了不匹配的资料。非常少的患者年龄超过 80 岁 (占所有资料的 0.5%， rtPA 资料的 1%)。主要的预测变量中存在着不平衡，有些结局的测量并没有完全使用盲法。所有溶栓药物的结局相似，但我们只关注 rtPA 的资料 (见表)。

在 rtPA 的研究中，症状性和致死性颅内出血 (ICH) 显著性增加，但总的早期和晚期死亡率的增加无显著性差异 (如 7-10 天，3 个月死亡率，见表)。如果从早期死亡中去掉致死性 ICH，则 rtPA 显著减少非 ICH 所致死亡所占的比例，可见致死性 ICH 占了 rtPA 治疗早期死亡的大多数。并且，在发病后 7-10 天仍然生存的患者中，rtPA 治疗不会导致死亡继续增加。

rtPA 明显降低卒中发病后 3 个月改良 Rankin 评分 (mRS) 3-6 分患者的比例 (见表)。从绝对数字来看，
每 1000 名发病 6 小时内溶栓的患者中，随访中死亡或残疾的患者减少了 60 名 (95% CI，30-90)。然而，溶栓效应有明显的异质性 (所有溶栓药物，$I^2$ 38%，$P=0.04$；rtPA 的试验，$I^2$ 62%，$P=0.007$)。随机效应模型分析得出更弱的阳性结果，尽管仍然具有统计学意义。另外，rtPA 明显降低生存者 (mRS 3-5 分) 的生活依赖，且无异质性。

定义 3 个月时 mRS 2-6 分为 “差的结局”，比定义 mRS 3-6 分为 “差的结局” 更易于得出溶栓改善神经功能的阳性结果 (注意这种分析仅限于那些同时提供了两种数据的试验)。然而，采用 mRS 2-6 分时具有明显的异质性，而采用 mRS 3-6 分却几乎没有，表明定义 mRS 3-6 分为 “差的结局” 可能提供更谨慎而有力的 rtPA 效果评估。

某些因素能够调整溶栓的效果和解释异质性。须慎重看待这些间接比较的结果，应该将其认为是产生的假设而不是确凿的证据 (注意 Wardlaw 等人的全部资料)。例如，在卒中 4 个小时内给予 rtPA，对于减少死亡或依赖似乎更有效，但是 3-6 个小时内治疗仍然有益处 (见表)。轻度卒中的患者 (NIHSS 评分 10-15 分) 可能从溶栓中得到最大的益处，严重的卒中患者 (NIHSS 评分 18-30 分) 受益最小，但是这些分析都建立在小样本量的基础上。数据不足以检测溶栓治疗对 CT 所见梗死灶的影响。虽然各研究之间存在的影像学以外的差异使直接比较很困难，但是仍然可以看到，用磁共振弥散 / 灌注成像不匹配筛选患者的研究结果和用普通 CT 筛选患者的结果是非常相似的。

**结果应用于临床实践**

使用 rtPA 的现行纳入标准，有可利用的证据支持，但是这些数据不足以决定临床上重要的亚组患者的危险 / 获益。特别是对于年龄超过 80 岁的患者，另外也受血管危险因素和卒中史、脑部扫描表现、卒中亚型以及时间窗的影响。

**进一步研究**

需要更多的数据来评价重要的亚组患者的整体受益程度，尤其是对于年龄在 80 岁以上的高龄患者，还有需要评价溶栓的时间窗，卒中严重程度的分级，卒中的亚型 (例如，腔隙，皮层)，糖尿病、高血压和既往卒中等合并症，阿司匹林使用情况，不同脑成像特征等。为了可靠地回答这些问题，特别是为了解释溶栓治疗个体化并使用于日益增长的病情复杂的卒中患者，需要来自于新的随机对照试验的更多数据。

**参考文献**


**关键词**：脑梗死，溶栓