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Thrombolysis in ischemic strokes with no arterial occlusion

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Abstract

Rationale—Twelve million people develop ischemic stroke each year world over and 30–40% of them do not have arterial occlusions at presentation. Trials conducted to study the efficacy of thrombolytic drug reported better outcome with use of thrombolytic drug but none studied the subtypes of ischemic strokes specifically and adequately. The subgroups of patients with no arterial occlusion at presentation continue to receive thrombolytic therapy without proven benefit and with some risk.

Aim—The aim of this article is to study whether intravenous thrombolysis with alteplase improves clinical outcome in ischemic stroke patients who do not have arterial occlusion at presentation.

Design—A retrospective medical record-based observational multicenter, multinational study.

Outcomes—Primary outcome measure would be clinical outcome at three-months from stroke onset measured by modified Rankin Scale and National Institute of Health Stroke Scale. Secondary outcome measure will be frequency of intracerebral hemorrhage causing worsening of clinical deficit defined as increase in National Institute of Health Stroke Scale by >4.

Keywords

angiography; arterial occlusion; ischemic stroke; lacunar stroke; thrombolysis

Introduction

Acute ischemic stroke patients often do not have vascular occlusion at the time of presentation to explain their clinical deficit, even within 4.5 h of symptoms onset. There are

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a few possibilities in such an instance. First, stroke was caused by vascular occlusion because of an embolus that had fragmented causing reopening of the vessel by the time the vessel was imaged. Second, stroke was a lacunar stroke caused by occlusion of a single deep penetrating artery small enough to be not seen with conventional vascular imaging (computed tomography [CT] or magnetic resonance imaging [MR] angiogram). Third, neurological syndrome was caused by vasospasm that resolved by the time vascular imaging was done. Fourth, symptoms were manifestation of a nonvascular etiology.

Thrombolytic therapy is definitely not indicated in the latter two cases, but whether it is beneficial in the former two cases has not been studied.

Need for study

The incidence of lacunar strokes has been uniformly reported to be around 20–30% of ischemic strokes by stroke registries from world over (1–4), and percentage of ischemic strokes because of large infarcts without vessel occlusion at presentation because of spontaneous recanalization is estimated to be around 15% from analysis of various studies (5).

Lacunar strokes, as discussed in detail below, are caused by small vessel disease due to lipohyalinosis and microatheroma (6,7), which is unlikely to respond to thrombolytic ('fibrinolytic') agent because thrombolytic drug act by lysing erythrocyte- and fibrin-rich thromboemboli. Lipohyalinosis is a disease of the vessel wall caused by raised arterial pressure that alters the integrity of walls of small vessels, leading to the appearance, focally in the subintima of fibrinoid and as the process advances, the integrity of the elastica and media is lost and there is widespread deposition of fibrous connective tissue causing occlusion of the lumen of the vessel (7). Necropsy studies have not shown occlusive erythrocyte –fibrin-rich thrombi in lacunar strokes, which are the target of thrombolytic agents. Large infarcts with no vessel occlusion are most likely embolic with spontaneous recanalization of vessel because of fragmentation of emboli (5,8) making use of thrombolytic agent potentially unnecessary and introducing a higher-than-average risk of hemorrhage. Thrombolytic agents in such case are posited by some to improve the microcirculation (9), but whether they actually do so and improve the clinical outcome remains to be tested.

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study reported a favorable outcome in patients treated with thrombolytic agent, alteplase at three-months from stroke onset leading to US Food and Drugs Administration approval of the drug. However, vascular studies were not reported in NINDS trial, and the number of patients in each subgroup was small leading to underpowered analysis to suggest beneficial effect in each of the tissue plasminogen activator (TPA) treated subgroup (51 patients in treatment arm vs. 30 patients in control arm in lacunar stroke subgroup). A committee that reviewed the NINDS trial results reported that the stroke subtype results were not valid (10). None of the other large randomized therapeutic trials required vascular imaging or analyzed outcomes according to vascular lesions (11,12). The question whether acute stroke patients without arterial occlusion should be treated with thrombolytic agent has not been studied well or resolved yet (9,10).

This suggests that there is large proportion of patients (30–40% of ischemic stroke) who receive thrombolytic therapy leading to exposure to the risk of complications from such therapy particularly intracerebral bleeding without a clear evidence of benefit. Each dose of intravenous thrombolytic agent costs around US\$2500 adding a huge financial burden from a therapy of unknown benefit in this group of patients. In developing countries like India, many patients do not possess medical insurance and hence pay the medical expenses by themselves. High cost of the drug and expectations arising from thereof, make the cost to benefit ratio all the more concerning and pertinent.

Methods

We propose to do a retrospective medical record-based observational multicenter, multinational study.

A retrospective analysis of data of patients will be done who presented to participating centers during past five-years, namely June 2006 to May 2011 with ischemic stroke diagnosed by clinical examination and imaging (CT or MRI) with National Institute of Health Stroke Scale (NIHSS) >4 and no imaging (CT or MR angiogram) evidence of vascular occlusion.

Such patients will be divided into two groups – one who received thrombolytic therapy and the other who did not.

Patients who had preexisting morbidities, which had significantly impaired their functionality defined as modified Rankin Scale (mRS) of 2, would be excluded from the study.

Size and location of the infarct will be determined by MR diffusion-weighted images.

Patients will be further subdivided into four groups:

- patients with cortical infarcts;
- patients with subcortical, thalamic, pontine infarcts with maximum diameter >20 mm;
- patients with midbrain, medullary, and cerebellar infarcts; and
- patients with subcortical, thalamic, pontine infarcts with maximum diameter <20 mm.

The first three groups will be considered to be caused by large vessel/embolic occlusion followed by spontaneous recanalization, and the fourth group will be considered as lacunar stroke.

Demographics, clinical syndrome, and risk factors of all the patients will be documented using a standardized data record form.

Sample size

Cumulative target sample size in this part of study would be 100 patients in each group.

This part will serve as a pilot study, and based on results from this study, a larger prospective study would be designed.

Inclusion criteria

Patients with following features will be included in the study:

- acute ischemic stroke diagnosed by clinical examination by a neurologist and imaging (CT/MRI) evidence of lesion corresponding to clinical deficit;
- no evidence of arterial occlusion on CT or MR angiogram at presentation; and
- MR diffusion imaging obtained within 48 h of onset of stroke.

Exclusion criteria

- demonstration of corresponding vascular occlusion or intracerebral bleed by CT/MRI and
- preexisting morbidity leading to reduce functionality defined as mRS ≥ 2 .

Primary outcome measure

Primary outcome measure would be clinical outcome at three-months from stroke, which would be measured by mRS and NIHSS because of their reliability, familiarity to the neurologic community, and comparability with end-points used in other trials of thrombolytic therapy.

mRS ≤ 2 at three-months would be termed as good outcome, while drop in NIHSS score of ≥ 4 would be termed as improvement.

Clinical outcomes of similar subgroups will be compared against each other.

Secondary outcome measure

Secondary outcome measure will be incidence of intracerebral hemorrhage leading to worsening of clinical deficit defined as increase in NIHSS by ≥ 4 .

Data collection

Data would be collected in a standardized data record form by certified examiners.

NIHSS and mRS will be recorded at discharge of patient from hospital or seven-days from ictus, whichever is earlier, at 30 days and at 90 days.

Statistical analysis

The primary outcome measurement will be mRS; it will be dichotomized into good outcome (0–2) or poor outcome (≥ 3). A chi-square test will be done to test the difference between groups that was treated with alteplase vs. the group that was not treated with alteplase. A further logistic regression will be conducted to model the good outcome with independent variables such as age, NIHSS at baseline, ethnicity, and group (alteplase vs. no alteplase). A similar test will be conducted on NIHSS and secondary outcome variable – incidence of

intracerebral bleed. NIHSS will be dichotomized into improvement as NIHSS drop >4 points or no improvement. Likewise, incidence of intracerebral bleed will be dichotomized as present or absent. Analysis will be done with Statistical Analysis Software (SAS 9.2 version, SAS Institute, Cary, NC, USA).

Summary

Thrombolysis in ischemic stroke with no arterial occlusion is a study designed to answer whether thrombolytic drugs are effective in two subgroups of ischemic stroke patients, namely embolic stroke with spontaneous recanalization and lacunar stroke. A shortcoming of all the major thrombolytic drug trials has been that they did not sufficiently study outcomes in individual subtypes of ischemic strokes in patients with thorough vascular imaging. The data collected was insufficient to subclassify ischemic stroke appropriately in post hoc analysis. Henceforth, this question remains unanswered. We plan to do a retrospective observational medical record-based study to serve as a pilot for a larger prospective study. Challenges faced by us are many. For example, dearth of patients, who were thrombolized and would meet inclusion and exclusion criteria, unavailability of required data especially the three-month follow-up examinations and MR imaging, lack of personnel for data collection preventing various centers to participate, and inability to procure funds for the study because of unavailability of data to support the claim. We use this journal as a platform to invite centers to join us in studying this important and understudied subject.

References

1. Bejot A, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, Di Carlo A, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. *Stroke*. 2008; 39:1945–51. [PubMed: 18436869]
2. Bogousslavsky J, Van Melle G, Regli J. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke*. 1988; 19:1083–92. [PubMed: 3413804]
3. Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, Pessin MS, et al. Harvard Cooperative Stroke Registry: a prospective registry. *Neurology*. 1978; 18:754–62. [PubMed: 567291]
4. Wang Y, Cui L, Ji X, Dong Q, Zeng J, Wang Y, Zhou Y, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. *Int J Stroke*. 2011; 6:355–61. [PubMed: 21609414]
5. Kassem-Moussa H, Graffagnino C. Non occlusion and spontaneous recanalization rates in acute ischemic stroke. A review of cerebral angiography studies. *Arch Neurol*. 2002; 59:1870–3. [PubMed: 12470173]
6. Horowitz DR, Tuhim S, Weinberger JM, Rudolph SH. Mechanisms in lacunar infarction. *Stroke*. 1992; 23:325–7. [PubMed: 1542890]
7. Fisher CM. Cerebral miliary aneurysms in hypertension. *Am J Pathol*. 1971; 66:313–30. [PubMed: 5009976]
8. Arnold M, Nedeltchev K, Brekenfeld C, Fischer U, Remonda L, Schroth G, et al. Outcome of acute stroke patients without visible occlusion on early arteriography. *Stroke*. 2004; 35:1135. [PubMed: 15073404]
9. Caplan LR, Mohr JP, Kistler JP, Koroshetz W. Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? Thrombolysis – not a panacea for ischemic stroke. *N Engl J Med*. 1997; 337:1309–10. [PubMed: 9345084]

10. Ingall TJ, O'Fallon M, Asplund K, Goldfrank LR, Hertzberg VS, Louis TA, Christianson TJ, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke*. 2004; 35:2418. [PubMed: 15345796]
11. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute stroke. *JAMA*. 1995; 274:1017–25. [PubMed: 7563451]
12. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). *Lancet*. 1998; 352:1245–51. [PubMed: 9788453]