Thrombolysis for acute ischaemic stroke


Introduction

The majority of strokes are ischemic (blockage of an artery in the brain by a blood clot). Prompt treatment with thrombolytic drugs can restore blood flow before major brain damage has occurred and improve recovery after stroke in some people. Thrombolytic drugs, however, can also cause serious bleeding in the brain, which can be fatal. Thrombolytic drugs derive from naturally-occurring enzymes that dissolve thrombus as part of the natural clotting cascade. Some are extracted from biological samples (e.g., urokinase, desmoteplase) and others are manufactured (e.g., recombinant tissue plasminogen activator (rt-PA), or recombinant pro-urokinase). The issues that are unclear are the age limit for use of these drugs and the time interval between a stroke and administration of the drug that results in benefit.

Objectives and methods

The authors sought to determine whether, and in what circumstances, might thrombolytic therapy be an effective and safe treatment for acute ischaemic stroke. They reviewed twenty seven randomised trials (thrombolytic agent compared with control in people with definite ischaemic stroke) from 1966 to 2013 from multiple databases.

Results

Twenty seven trials were included, involving 10,187 participants, testing urokinase, streptokinase, rt-PA, recombinant pro-urokinase or desmoteplase. Four trials used intra-arterial administration, while the rest used the intravenous route. Most data came from trials that started treatment up to six hours after stroke. About 44% of the trials (about 70% of the participants) were testing intravenous rt-PA.

Thrombolytic therapy, mostly administered up to six hours after ischemic stroke, significantly reduced the proportion of participants who were dead or dependent (modified Rankin 3 to 6) at three to six months after stroke. Thrombolytic therapy increased the risk of symptomatic intracranial haemorrhage, early death and death by three to six months after stroke. Early death after thrombolysis was mostly attributable to intracranial haemorrhage. However the overall benefits outweighed the risks.

Treatment within three hours of stroke was more effective in reducing death or dependency without any increase in death. Trials testing rt-PA showed a significant reduction in death or dependency with treatment up to six hours (OR 0.84, 95% CI 0.77 to 0.93, P = 0.0006). Treatment within three hours was more beneficial (OR 0.65, 95% CI 0.54 to 0.80, P < 0.0001). Participants aged over 80 years benefited equally to those aged less than 80 years, particularly if treated within three hours of stroke.

Authors’ conclusions

- Thrombolytic therapy given up to six hours after stroke reduces the proportion of dead or dependent people.
- Those treated within the first three hours derive substantially more benefit than with later treatment.
- There was an increase in symptomatic intracranial haemorrhage, deaths on follow-up but the overall benefit was greater than the risk.
- There appears to be no upper age limit – persons older than 80 years also benefit from thrombolytic therapy.

Expert Comments from CMC faculty: Dr. Sanjith Aaron, Professor, CMC Vellore

Stroke may be defined as an abrupt onset focal neurological deficit which cannot be explained by any other cause other than that of vascular origin. 80% to 85% of the strokes are ischaemic and 15% to 20% are haemorrhagic. Stroke management has moved forward tremendously, and includes antiplatelet drugs, Heparin and Thrombolytic therapy.

Reperfusion therapy is the only definitive therapy in the management of stroke. Reperfusion may be done using intravenous or intra-arterial thrombolysis and mechanical thrombectomy. In CMC, the therapeutic window used is 4.5 hours from the time. Beyond 4.5 hours, intra-arterial thrombolysis may be beneficial in some specific situations. Thrombolysis is not given for those below 18 years as the etiological factors are different in the young. There is no fixed upper age limit. Patients above 80, if they were fully functional before the stroke, are eligible candidates provided there are no contraindications.