Optimizing thrombolysis in acute ischaemic stroke

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Link to publication

Citation for published version (APA):
CHAPTER 2

ANTIPLATELET THERAPY IN COMBINATION WITH RT-PA THROMBOLYSIS IN ISCHAEMIC STROKE (ARTIS): RATIONALE AND DESIGN OF A RANDOMISED CONTROLLED TRIAL

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Cerebrovasc Dis 2010;29:79–81. PMID 19907167
ABSTRACT

Background
Intravenous thrombolysis (IVT) is currently the only approved treatment for acute ischaemic stroke. After IVT induced recanalisation, reocclusion is observed in 20–34%, probably caused by platelet activation. In acute myocardial infarction, the combination of IVT and antiplatelet therapy leads to better outcome compared to IVT alone. In patients with acute ischaemic stroke, several studies showed that patients on antiplatelet treatment prior to IVT had an equal or even better outcome compared to patients without antiplatelet therapy, despite an increased risk of bleeding.

Methods
We present the protocol of a multicenter randomised clinical trial (n=800) investigating the effect of the early administration of aspirin in patients treated with IVT for acute ischaemic stroke on functional outcome. Primary endpoint is favourable outcome, defined as a modified Rankin scale score of 0–2 at 3 months.

Conclusion
This study will answer the question whether early administration of aspirin improves outcome in patients treated with IVT for acute ischaemic stroke.
BACKGROUND

Stroke is an important cause of death and acquired disability in the industrial world. Current standard treatment in acute ischaemic stroke is intravenous thrombolysis (IVT) with alteplase (or recombinant tissue plasminogen activator, rt-pa). Alteplase aims to break down the fibrin clot in order to restore recanalisation of the occluded artery. Within the time window of 4.5 hours, early recanalisation is associated with improved functional outcome and reduced mortality.\(^1,2\) Unfortunately, efficacy of IVT is only modest. The overall recanalization rate after IVT was only 46% in a meta-analysis.\(^2\) Reocclusion after initial recanalization partly contributes to this low rate. In studies with continuous transcranial Doppler monitoring early reocclusion occurred in 20–34% of patients treated with IVT.\(^3,4\) In these studies, reocclusion accounted for twothird of the cases with early neurological deterioration after initial improvement.\(^3,4\) A recent study confirmed the association between reocclusion and clinical deterioration and showed that early reocclusion is highly predictive of long-term poor outcome.\(^5\)

Reocclusion after IVT is probably initiated by increased platelet activation. Therefore, the addition of antiplatelet therapy to IVT might prevent reocclusion. In patients with myocardial infarction, the results of the second International Study of Infarct Survival (ISIS-2) showed that mortality after acute myocardial infarction was reduced by 42% if patients were treated with the combination of streptokinase and aspirin, compared to a 25% reduction in patients who were treated with streptokinase alone.\(^6\)

The Multicenter Acute Stroke Trial-Italy duplicated the design of the ISIS-2 in patients with ischaemic stroke and showed an absolute risk reduction of 12% for disability in survivors treated with the combination of streptokinase and aspirin compared to treatment with streptokinase alone.\(^7\) However, this benefit was outweighed by an excess in mortality mainly due to symptomatic intracerebral haemorrhage (SICH) in the group with combined treatment. These results have contributed to the fear of combining antiplatelet agents with IVT in patients with acute ischaemic stroke. Therefore, the early administration of aspirin in patients treated with alteplase has never been investigated. For safety reasons, the
pivotal Neurological Institute of Neurological Disorders and Stroke (NINDS) trial did not allow administration of antiplatelet therapy within the first 24 hours after IVT. However, long-term use of antiplatelet therapy was not a contra-indication for inclusion in this trial. Subgroup analysis of this NINDS trial showed that previous aspirin use was associated with a better outcome, lower frequencies of early neurological deterioration, and similar SICH rates as compared to patients with no previous aspirin use. Given the association between early neurological deterioration and reocclusion on the one hand and the less frequent use of prior antiplatelet therapy on the other hand, one might argue that previous antiplatelet therapy prevents reocclusion. This suggestion is supported by several cohort studies investigating the relationship between prior antiplatelet therapy and IVT. Despite the increased risk of SICH after IVT in patients using antiplatelet agents, outcome was equal or even better compared to patients with no antiplatelet therapy. The association between antiplatelet therapy and SICH was not confirmed by other studies. Based on all these observations, we hypothesize that immediate addition of antiplatelet therapy to IVT in patients with acute ischaemic stroke improves outcome by enhancing clot lysis and preventing reocclusion after initial recanalisation. We expect this benefit will outweigh a possibly slightly increased risk of SICH.

METHODS AND OUTCOME

The Antiplatelet therapy in combination with Rt-PA Thrombolys in Ischaemic Stroke (ARTIS) Trial is a multicenter randomised controlled open label trial with blind endpoint assessment in patients receiving IVT for acute ischaemic stroke. Patients already on antiplatelet therapy are excluded. We compare administration of intravenous aspirin within 90 minutes after start of IVT with standard treatment, in which antiplatelet therapy is usually postponed for 24 hours after IVT. The primary objective is to investigate whether the immediate addition of aspirin to standard rt-PA thrombolysis improves favourable outcome at 3 months (modified Rankin scale score of 0–2). ARTIS aims to detect an improvement of 10%, which requires a sample size of 800 patients. Among secondary endpoints is
SICH, defined as neurological deterioration of ≥4 points increase on the National Institutes of Health Stroke Scale in combination with intracranial haemorrhage on follow-up CT scan without other obvious causes for the deterioration. With regard to the potential safety risks, the Data Safety Monitoring Board will perform ongoing safety surveillances and analysis of effectiveness of unblinded data during the trial. The trial started in July 2008. As of October 2009, 36 Dutch centres are participating in ARTIS of which 24 are currently recruiting patients. So far, 189 patients have been included. Foreign sites are kindly invited to participate.

CONCLUSION

This ARTIS trial will answer the question whether the early administration of aspirin improves outcome in patients treated with IVT for acute ischaemic stroke. The trial intervention comprises a simple and cheap adjustment of current antiplatelet regimen in acute stroke.

ACKNOWLEDGMENTS

The ARTIS trial is funded by the Dutch Heart Foundation (DHF-2005B118). Trial registration: the Netherlands National Trial Register NTR 822.

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REFERENCES
