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REVIEW

Safety of Carotid Intervention Following Thrombolysis in Acute Ischaemic Stroke

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WHAT THIS PAPER ADDS

Urgent carotid intervention is indicated for stroke resulting from significant carotid stenosis, but performing such intervention soon after thrombolysis may be associated with increased risk of bleeding and other complications. By analysing the 30-day stroke or death rates in published series of patients who have undergone carotid intervention within 14 days of thrombolysis, this systematic review concludes that early carotid endarterectomy post-thrombolysis appears to be safe, with stroke or death rates similar to that of surgery without thrombolysis.

Objectives: Thrombolysis is effective in improving clinical outcome in the treatment of acute ischaemic stroke. However, thrombolysis results in low recanalisation rates, particularly in the event of carotid occlusion. Carotid intervention is indicated in stroke resulting from significant carotid atherosclerosis, but intervention soon after thrombolysis may be associated with increased risks. This study aims to assess the safety of carotid intervention post-thrombolysis for acute ischaemic stroke.

Design: Systematic review.

Materials and methods: MEDLINE and EMBASE were searched on 29 May 2014. Inclusion criteria were (i) intra-arterial or intravenous thrombolysis for acute ischaemic stroke; (ii) carotid intervention within 14 days of thrombolysis; and (iii) derivable primary outcome. The primary outcome was 30-day stroke or death. A meta-analysis of incidence was completed for the 30-day stroke or death rates using Freeman–Tukey arcsine transformations and assuming random effects. Point estimates with confidence intervals (CIs) were generated and heterogeneity was assessed. The strength of recommendations and quality of underlying evidence were assessed using the American College of Chest Physicians (ACCP) grading system.

Results: Nine included publications recorded 114 carotid endarterectomy (CEA) and four angioplasty interventions. The point estimate of 30-day stroke or death for CEA was 4.93% (95% CI 1.83–9.44), representing four of 114. The strength of recommendation and quality of underlying evidence for CEA as per the ACCP grading system was determined as 1C. There were no cases of stroke or death in patients undergoing angioplasty post-thrombolysis (0/4).

Conclusions: Early CEA post-thrombolysis appears safe, with stroke or death rates similar to that of the operation without thrombolysis. However, the wide CI obtained highlights the uncertainty of this result. Further, we emphasise that this recommendation is supported by low-quality evidence. Additional data are required to confirm the safety of surgery and early endovascular therapy post-thrombolysis.

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INTRODUCTION

Acute ischaemic stroke is a leading cause of death and disability worldwide.[1] According to the World Stroke Organization, one in six people will have a stroke in their lifetime, with a mortality rate of 25% in the first year.[2,3]

Thrombolysis has revolutionised ischaemic stoke therapy with the potential to acutely reverse symptomatology and permit complete recovery.[2] The most well-studied drugs for thrombolysis, including streptokinase, urokinase, and recombinant tissue plasminogen activator, work by converting plasminogen to plasmin to break down fibrin in blood clots.[2]

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While thrombolysis has become established as the standard therapy in acute ischaemic stroke,[4] partial or complete recanalisation following thrombolysis only occurs in approximately 10% of occluded internal carotid arteries and in 25% of occluded proximal middle cerebral arteries.[5,6] Further, more than 80% of stroke patients with a National Institutes of Health Stroke Scale score of $\geq$10 have persistent arterial occlusion despite thrombolysis.[7] In such circumstances, and/or in the presence of significant carotid stenosis, it is important to consider early operative intervention.

Carotid intervention, including carotid endarterectomy (CEA) and angioplasty, is indicated in symptomatic carotid stenosis of 50—99%, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria,[8] or 70—99%, according to the European Carotid Surgery Trialists' (ECST)[9] Collaborative Group criteria, within 2 weeks of onset of stroke or transient ischaemic attack symptoms.[10] With the risk of recurrent ischaemic attack being highest within the days following the first episode,[11] there has been a recent move towards performing carotid intervention as soon as possible after the onset of symptoms.[12—14] Recent evidence suggests no additional procedural risk if the intervention is performed in the hyperacute period, whether this time period is defined as $<$48 h, $<$7 days, or $<$14 days.[13]

However, thrombolysis up to 6 h after the onset of stroke has been found to increase the risk of symptomatic and fatal intracranial haemorrhage approximately fourfold within the first 7 days, even after the clearance of thrombolysis.[15] Data from a recent meta-analysis have identified an incidence of symptomatic intracranial haemorrhage of 7.7% in patients treated with alteplase alone within 6 h for acute ischaemic stroke.[15] Therefore, while early carotid intervention is indicated in stroke resulting from carotid stenosis, performing carotid intervention soon after thrombolysis may be associated with an increased risk of bleeding and other complications.

This systematic review aims to assess the safety of carotid intervention post-thrombolysis by analysing the 30-day stroke or death rates in published series of patients who have undergone carotid intervention post-thrombolysis.

MATERIALS AND METHODS

Search strategy

A systematic review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was performed.[16] MEDLINE and EMBASE were searched using the Ovid portal. The databases were searched on 29 May 2014, for articles published between 1947 and 2014. The search string used was: [stroke **and** thrombolysis **and** carotid **and** endarterectomy] **or** [stroke **and** thrombolysis **and** carotid and (stent or angioplasty or intervention or thrombectomy)].

Two authors (R.M. and M.I.Q.) searched independently and compared results at each stage. A third author (A.H.D) arbitrated disagreements. Authors of cases presented in conference proceedings were contacted where further details were required. Data abstraction and quality assessment were conducted by two independent investigators (R.M. and M.I.Q.).

Inclusion and exclusion criteria

Studies were considered for summation analysis according to the following inclusion criteria: intra-arterial or intravenous thrombolysis for acute ischaemic stroke; carotid intervention within 14 days of thrombolysis; derivable primary outcome; intervention conducted on internal carotid artery; and internal carotid stenosis confirmed on imaging. Studies were excluded based on the following exclusion criteria: case series with fewer than five cases; review articles; non English-language studies; intraoperative thrombolysis; and intervention conducted on middle cerebral artery.

Primary and secondary outcomes

The primary outcome measure was 30-day stroke or death. Secondary outcome measures included bleeding complications; cranial nerve injury; and wound complications (defined as delayed healing or infection, or wound haematoma at site of surgery).

Analysis

The quality of studies was assessed in domains of study design; study duration; sample size; inclusion and exclusion criteria; diagnosis and follow-up by stroke neurologist; operative technical details; postoperative control of blood pressure; and source of funding. The strength of recommendations and quality of underlying evidence were assessed using the American College of Chest Physicians (ACCP) grading system, which is a modified approach to the international GRADE group.[17] The grading scheme classifies recommendations as strong (grade 1) or weak (grade 2), according to the balance between benefits, risks, burdens, and the degree of confidence in estimates of benefits, risks, and burdens. The system classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors that include study design, consistency of the results, and directness of evidence.

A meta-analysis of incidence was completed for the 30-day stroke or death rates using Freeman—Tukey arcsine transformations and assuming random effects as described by DerSimonian and Laird.[18] Point estimates with confidence intervals (CIs) were generated and heterogeneity was assessed. I^2 is reported, which is a measure of the degree of inconsistency in study results. I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance with values ranging from 0 to 100%. The I^2 value is proportional to the heterogeneity across studies, with a value of 0% representing no heterogeneity and larger values demonstrating increasing heterogeneity. I^2 is reported with 95% uncertainty intervals. Calculations were performed using MedCalc for Windows, version 13.1.2.0 (MedCalc Software, Mariakerke, Belgium).