IS IV TPA THE DEFINITE TREATMENT IN ACUTE LARGE ARTERY OCCLUSION?

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There are essentially 3 options for definitive treatment in acute large artery occlusions causing ischaemic stroke symptoms: iv rtPA, inta-arterial thrombolysis with pro-urokinase (if available) or rt-PA, or thrombectomy.

Evidence for benefit with iv rt-PA comes from at least 9 randomised trials, 8 of which were blinded with placebo control. These trials considered both functional benefit (3 month modified Rankin scale score) and safety (mortality and symptomatic haemorrhage rates) and could consider the balance between risk and benefit. Pooled analysis of these 8 trials offers compelling evidence of the net value of intervention, and a strong indication that onset to treatment delay has a crucial influence on outcome. Group analysis of all 9 trials also confirms net benefit, and lends support to the influence of treatment delay. Use of intravenous rt-PA has been approved by the drug regulatory authorities in most regions. Staff have been trained and services have been configured to provide treatment in most developed healthcare systems, though costs still limit use in certain countries, and treatment rates have been improving year on year. Despite the present wording of drug approval in Europe there is no evidence of any interaction of rt-PA treatment with age in determining outcome: according to RCT and other controlled studies the elderly derive equal benefit to younger patients, and treatment guidelines support this.

Subgroup analysis of the randomised trial data have so far failed to indicate that there is a clear relation between stroke severity and treatment response, except perhaps at the level of very mild stroke symptoms where benefit is less certain.

In contrast, the evidence supporting intra-arterial thrombolysis remains limited. The PROACT-II trial was positive and offers clear encouragement towards intra-arterial treatment but the control treatment was heparin rather than iv rt-PA, and marketing authorisation for pro-urokinase was not granted on the basis of the single randomised trial. In fact, recanalisation rates which are likely improved by intra-arterial treatment can be even better through use of thrombectomy devices. Certainly, patients with large artery occlusion in whom the clot extends more than a few millimetres seem unlikely to reperfuse with iv rt-PA.

There is excellent evidence showing high rates of recanalisation associated with various thrombectomy procedures. Further, there is compelling evidence associating successful recanalisation with better outcomes than are seen in non-reperfused patients. This is extrapolated by many clinicians into an incontrovertible argument that thrombectomy is the treatment of choice in large artery occlusion. This disregards crucial considerations.

There is no randomised evidence that takes into account safety as well as efficacy for thrombectomy: safety issues may limit the risk/benefit balance. There is evidence of an interaction between time to recanalisation and outcome for thrombectomy, just as for iv-rtPA. At best, there is a likely 60-120 minute delay in initiation of thrombectomy from the time of first patient contact. There is no guarantee that the postulated improved effectiveness of recanalisation with thrombectomy will outweigh the benefits of immediate iv treatment. Most neuroradiologists suggest an upper age limit for thrombectomy due to increasing risks, that is not necessary for iv treatment. Costs of thrombectomy devices are higher, and the costs and availability of organising a 24/7 service are substantial. Rapid interventional neuroradiology services are not organised in most countries and may be impractical to organise in many. The only trial that has tried to compare directly iv treatment against a strategy of intervention (IMS-III) was stopped for futility. Even if thrombectomy is proven to be effective and safe, research will still be needed to delineate the maximum time delay, age limits, optimal device, cost-effectiveness etc.

At present, iv rtPA remains the treatment of choice, despite encouraging indications that it may in future be supplanted for patients with large artery occlusion.