Weighing the impact of post hoc studies

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In their *JNNP* study, Dr Sun *et al* report post hoc analyses of data from the 'Minimally Invasive Surgery plus Alteplase for Intracerebral haemorrhage Evacuation trial (MISTIE III)'.[1 2] The parent study was a randomised open-label trial comparing image-guided minimally invasive haematoma evacuation followed by alteplase irrigation (MIS+alteplase) to standard medical care. The primary endpoint of the MISTIE-III was a good functional outcome defined as the proportion of patients who achieved a modified Rankin Scale score of 0–3 at 1 year. This post hoc study focused on 310 subjects (62% of the MISTIE-III study population) with intraventricular haemorrhage (IVH) to determine the effect of MIS+alteplase on the change in IVH volume, disability and mortality. The authors found that although there was a greater reduction in IVH volume in the MIS+alteplase arm, there was no significant difference in functional outcomes between the intervention and control groups. It is reassuring that the findings were congruent with a similar post hoc analysis from the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Haemorrhage trial.[3]

'Post hoc' is Latin for 'after this'. Post hoc analyses typically examine a subset of trial subjects for endpoints discrete from the primary outcome. These analyses occur after the predefined primary analysis of data and do not benefit from the bias mitigation afforded by randomisation. Post hoc analyses lack the rigour to minimise false-positive findings and false-negative findings. Prespecified significance levels are useful to avoid making false discoveries, but when multiple comparisons are performed, the risk of a false-positive inference increases with the number of tests. Most post hoc analyses do not correct for multiple comparisons.

Statistical analyses on the IVH subgroup of MISTIE-III consisted of three main comparisons: the association between intervention and the change in IVH volume, the association between delta IVH and poor functional outcome and the association between delta IVH and mortality. Prespecified analyses stratifying by baseline intracerebral haemorrhage volume and location were also performed to adjust for baseline severity. An alpha level of 0.05 defined statistical significance, and there was no adjustment for multiple comparisons.

Post hoc analyses may lack the experimental design rigour of the parent trial, but they do add to the body of scientific evidence, provided the inherent limitations of the methodology are recognised. Results should be considered exploratory and may be hypothesis generating. Post hoc findings can elucidate outcomes that were not anticipated at the time of trial design and, therefore, are useful to inform future research.

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