Thrombolysis for acute stroke in Australia

Brendon J Smith

To the Editor: Waxman's prompt recovery after a stroke was probably a stroke of luck,[1] unless perhaps Saint Mary MacKillop was involved. Amid the conflicting evidence on the effect of thrombolysis on recovery in ischaemic stroke, one fact is beyond doubt — thrombolysis gives no greater improvement at 24 hours than placebo.[2] It is the various measures of recovery at 3 months, and the risks of adverse outcomes from protocol violations in administering thrombolysis, that are less clear.

The European Cooperative Acute Stroke Study III (ECASS III) showed that there is a benefit from administering thrombolysis up to 4.5 hours after stroke onset,[3] and the complete Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register (SITS-ISTR) data showed that this benefit can be reproduced in non-trial hospital practice.[4] Simpson and colleagues say that the Australian data support this conclusion, even though outcomes show slightly higher mortality compared with rest-of-world data.[5]

There are several gaps in that line of reasoning. A modified Rankin score (mRS) of 0–1 (zero or minimal disability) is the standard measure of a good outcome. In ECASS III, an mRS of 0–1 was seen in 52.4% of patients who received thrombolysis compared with 45.1% of patients who received placebo.[3] However, the SITS-ISTR data showed an mRS of 0–1 in just 40% of patients treated within 3 hours of stroke onset and 44% of patients treated at 3–4.5 hours.[4] This is despite lesser stroke severity (National Institutes of Health Stroke Scale score: 10 in the SITS-ISTR cohort v 11.6 in the ECASS III placebo group), selective patient inclusion, and exclusion of patient data with protocol violations known to give worse outcomes.

Achieving a worse result than placebo is hardly evidence for safe and effective use of thrombolysis in normal clinical practice.

However, the Australian study presents the data differently, using an mRS of 0–2 and thereby concluding good outcomes in patients with greater disability than is the accepted good outcome measure.[5] Rather than providing the actual data and the percentage of patients with good outcomes, a novel measure of odds ratio comparison with rest-of-world data is made.

Publishing data in the same format as for the full SITS-ISTR report would allay concerns of what may be unfavourable outcomes compared with clinical trial data. Patients deserve to be told what their likely prognosis will be in hospitals that are less experienced in stroke thrombolysis than The Alfred, where Waxman received world-class stroke care.

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In reply: We were delighted to hear of Waxman's "miraculous" recovery, and admire the world-class standard of stroke care which was delivered at The Alfred.[1] The Australian data in the Safe Implementation of Thrombolysis in Stroke (SITS) database up to 2008 included tertiary referral centres and outer metropolitan hospitals, and centres with varying experience of using recombinant tissue plasminogen activator (rt-PA) in clinical practice. There was no difference in outcomes according to experience of the treating centres. We believe that the non-trial clinical data presented in our article are a realistic indication of expected outcomes for all patients receiving thrombolysis for stroke in Australia.

The choice of a modified Rankin score (mRS) of 0–2 as an outcome measure in our article was largely dictated by the SITS international analysis. The aim of our study was to compare outcomes in Australia with those in the rest of the world; these were also not significantly different when an mRS of 0–1 was used as an outcome measure (mRS 0–1 at 3 months, 34.6% for Australia v 37.8% for the rest of the world; $P = 0.13$).

The original National Institute of Neurological Disorders and Stroke (NINDS) trial data,[2] now more than 15 years old, have been analysed and re-analysed and, arguably, it is time to move on from rehashing the data. However, if one wishes to follow this path, there was in fact a significant difference in improvement at 24 hours between patients in the rt-PA and placebo groups. Smith's statement that thrombolysis gives no greater improvement at 24 hours than placebo is correct in terms of the proportion of patients with an improvement in National Institutes of Health Stroke Scale (NIHSS) score of 4 or more, but this is a low benchmark and many untreated patients also show a relatively mild improvement at 24 hours. If one considers major neurological improvement (MNI, defined as an improvement in 24-hour NIHSS score of 8 or more), this was seen in a greater proportion of patients in the rt-PA group compared with the placebo

group.[3] Patients with MNI have a much greater chance of achieving minimal or no disability at 3 months, which is by far the most accepted outcome measure for thrombolytic therapy. This major early recovery is frequently seen in patients who receive rt-PA, and has been termed the "Lazarus effect". Waxman was fortunate enough to experience this effect — but it occurs far too often with rt-PA in stroke to pass the Catholic Church criteria for a miracle.

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