Reduction of iron neurotoxicity in intracerebral haemorrhage

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The chances of recovering from acute spontaneous intracerebral haemorrhage, the most serious form of acute stroke, depend on the location, extent, and degree of bleeding.[1] However, a substantial amount of data from animal studies also suggests that prognosis is related to the toxic effects of iron and other haemoglobin breakdown products from the immuno–inflammatory response, which manifest clinically in the extent of perihaematomal oedema during subsequent days.[2] In *The Lancet Neurology*, Magdy Selim and coauthors report results of the Intracerebral Haemorrhage Deferoxamine (i-DEF) trial,[3] in which they tested the safety and efficacy of the iron chelator deferoxamine mesylate in a prospective, multicentre, randomised, placebo-controlled, double-blind phase 2 trial of 294 patients, who were enrolled within 24 h of the onset of primarily supratentorial intracerebral haemorrhage.

The i-DEF investigators used a novel approach to test for futility for the likelihood that a treatment effect could be readily identified in a future phase 3 trial. At 90 days, the conventional timepoint for assessment of the primary outcome in acute stroke trials, 48 (34%) of 140 patients in the deferoxamine mesylate group and 47 (33%) of 143 in the placebo group had a good clinical outcome, which was defined as a score of 0–2 on the modified Rankin Scale. Because the 90% upper confidence bound for the absolute difference between the groups of 6·8% fell below the prespecified 12%, these results suggest that it would be futile to proceed to a phase 3 trial. However, deferoxamine mesylate was shown to be safe, and a potential treatment effect was suggested at 180 days, when the 90% upper confidence bound (15·6%) for the absolute risk difference of 8·6% was higher than the specified futility margin.

The setting of the futility margin was somewhat arbitrary, but the i-DEF analyses were arguably too stringent to detect an effect similar in magnitude to that of intravenous alteplase for the treatment of acute ischaemic stroke. As many researchers have bitterly experienced, smaller net beneficial effects are more plausible for acute intracerebral haemorrhage, and thus trials should be designed to detect smaller effects.[4–6] Testing of a smaller treatment effect might have avoided the quandary of whether to proceed to another clinical trial on the basis of the emergence of a potential treatment effect at 180 days, especially given that deferoxamine mesylate is cheap and could potentially be widely used. Although the finding of an increased proportion of patients with good clinical outcomes at day 180 with deferoxamine mesylate compared with placebo supports previous findings suggesting that full recovery from intracerebral haemorrhage takes longer than that from acute ischaemic stroke,[6,7] the absence of any effect on the other standard clinical outcomes (such as neurological and cognitive function at day 90), or on in-hospital measures of perihaematomal oedema, is somewhat disconcerting. Although time to initiation, dose, and duration of treatment were carefully chosen, post-hoc exploratory analyses suggested an interaction of the treatment effect with time-to-treatment. Because less than a third of patients received deferoxamine mesylate within 12 h of the onset of symptoms, the drug might not have been able to affect the cascading pathways of injury related to iron deposition.

Thus, better understanding of the mechanisms of perihaematomal oedema and of how best to quantify changes in this important surrogate marker to allow for earlier and more efficient testing of potential anti-oedema treatments are needed. It seems risky to retest deferoxamine mesylate alone in a phase 3 trial without more data, but perhaps the combination of the drug with another plausible intervention, such as antihypertensive drugs[4] or tranexamic acid,[5] might result in an overall beneficial effect. The component effects of each part of the intervention could subsequently be unpacked to identify the main efficacy drivers. Such a combination approach—involving early blood pressure, glycaemic and fever control, and reversal of anticoagulation—is being tested in INTERACT3 (NCT03209258). Another approach is to commence treatments much earlier, within just a few hours of the onset of intracerebral haemorrhage, such as in a new trial, FASTEST, of recombinant blood-coagulation Factor VIIa in patients who are diagnosed in a modern CT-equipped mobile ambulance, which was recommended for funding by the US National Institutes of Neurological Diseases and Stroke Council in February, 2019 (Broderick J, University of Cincinnati, Cincinnati, USA,personal communication).

There is an urgent need to develop reliable evidence to guide the management of intracerebral haemorrhage worldwide.[8] Thus, the results of i-DEF will provide much

for discussion by delegates attending the forthcoming World Intracranial Haemorrhage Conference.

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The global burden of stroke: persistent and disabling

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According to a report from the Global Burden of Disease (GBD) 2016 Lifetime Risk of Stroke Collaborators,[1] the estimated global lifetime risk of stroke in 2016 for those aged 25 years or older was 24·9%, an increase from 22·8% in 1990. The estimate includes an almost equal risk of stroke among women and men, and an 18·3% risk of ischaemic stroke and 8·2% risk of haemorrhagic stroke.[1] Furthermore, the lifetime risk varies by Socio-demographic Index (SDI; 23·5% for high SDI, 31·1% for high-middle SDI, and 13·2% for low SDI countries); the low risk in the low SDI group is attributed to the high numbers of competing causes of mortality. Additionally, the prevalence of stroke is expected to increase. In a policy statement crafted by an American Heart Association working group, it was concluded that, by 2030, almost 4% of US adults will have had a stroke, accounting for total direct annual stroke-related medical costs increasing from US$71·55 billion in 2012 to $183·13 billion by 2030.[2] Driving the upswing in stroke prevalence rates is a projected increase in stroke attributed to a growing and ageing population and lower stroke case fatality rates associated with better acute ischaemic stroke care and improved recurrent stroke prevention strategies.[2] These findings point to the importance of continued surveillance of stroke case fatality, incidence, and recurrence rates.[1,2]

In *The Lancet Neurology*, the GBD 2016 Stroke Collaborators[3] provide a systematic analysis of the global, regional, and national burden of stroke from 1990 to 2016 in terms of incidence, prevalence, deaths, years lived with disability, years of life lost, and disability-adjusted life-years (DALYs). Improvements on previous GBD stroke estimates include new approaches to collect inpatient hospital data, extension of the oldest age group for study (up to 95 years or older), a more comprehensive literature review, and the addition of expected values for all measures on the basis of socioeconomic development.

Notably, stroke remains the second leading cause of death worldwide, with 5·5 million (95% uncertainty interval [UI] 5·3–5·7) deaths attributed to this cause in 2016. Fewer women (2·6 million [2·5–2·7]) than men (2·9 million [2·8–3·0]) died from stroke.[3] Deaths due to ischaemic stroke were slightly less frequent than those due to haemorrhagic stroke. Stroke was also the second most common cause of DALYs. The highest incidence of stroke occurred in east Asia, followed by the eastern European region, whereas the lowest rates were in central Latin America. Women and men had similar age-specific incidences at ages up to 55 years, but the rates were greater in men at 55–75 years, levelling out at ages older than 75 years.

Most of the stroke burden was attributable to risks measured in GBD. For example, metabolic factors (high systolic blood pressure, body-mass index, fasting plasma glucose, and total cholesterol and low glomerular filtration rate) accounted for 72% of stroke DALYs, behavioural factors (smoking, poor diet, and physical inactivity) accounted for 66%, and environmental risks