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**Nerinetide: a potential neuroprotectant as adjunct to thrombectomy for acute stroke**

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Despite major benefits from thrombectomy, around 50% of treated acute stroke patients with large vessel occlusion have poor outcome, mainly because of already large ischaemic core when recanalization is achieved<sup>1</sup>. Protecting the ischemic penumbra using appropriate therapeutic means until reperfusion is achieved would stop or slow down infarct growth and hence result in improved functional outcomes<sup>2</sup>. Hill et al must be congratulated for completing ESCAPE-NA1, the first-ever randomized controlled trial evaluating a putative neuroprotectant, namely nerinetide, as adjunct to thrombectomy in acute stroke with proximal intracranial occlusion treated within 12h from stroke onset<sup>3</sup>.

Although it comes as a disappointment that the results of the trial are neutral, several points mitigate this negative outcome. First, the median duration of drug infusion before thrombectomy was only ~20mins (IQR ~8-20), which is short compared to estimated infarct growth ranges of 3-20mls/hr in similar populations<sup>4, 5</sup>. Accordingly, nerinetide would be expected on average to have saved a few mls of brain tissue at best. In the authors' seminal monkey study, drug infusion was started 30 min before recanalization in all animals<sup>6</sup>, whereas in the clinical trial it was <30 min in the majority of patients. Thus, patients with longer times to thrombectomy, such as those treated according to the 'drip-and-ship' paradigm, may significantly benefit from nerinetide if administered at the primary center. Second, based on the 'penumbra freezing' hypothesis<sup>2</sup>, benefit from nerinetide would depend on the volume of penumbra still present at time of drug administration. Although patient inclusion in ESCAPE-NA1 required moderate-to-good collaterals on CT angiography, perfusion imaging was not part of the selection criteria. Interestingly, nerinetide appeared to exert greater benefits in complete vs incomplete recanalization (their Figure 3), which would concur with the penumbra stabilisation concept<sup>2</sup>. In the primate study, complete recanalization was achieved in all subjects<sup>6</sup>, as compared to ~45% of the enrolled patients in the ESCAPE-NA1 trial. Third, as supported by subgroup analysis<sup>3</sup>, nerinetide may benefit patients not receiving intravenous thrombolysis (IVT) with alteplase prior to thrombectomy. Although, as supported by pilot data, this observation may reflect unexpected untoward drug-drug interaction, two alternative, or complementary, explanations may be considered: i) drug infusion time may have been shorter in the IVT as compared to the no IVT group; and ii) the observed trend for a greater drug effect in patients treated beyond, as compared to within, 6hrs from stroke onset (their Figure 3) may have favoured the no IVT subgroup. In addition, assuming the nerinetide-alteplase interaction is true, performing IVT prior to thrombectomy using tenecteplase instead of alteplase, which is supported by evidence from a randomized trial<sup>7</sup> and is considered safe and reasonable as per current American Heart Association guidelines<sup>8</sup>, may obviate this problem.

Overall, designing and conducting the ESCAPE-NA1 trial represented a major achievement for which Hill et al should be commended. However, this trial may not have fully exploited the potential penumbral stabilisation effects of nerinetide. Further trials are warranted before one can confidently conclude regarding nerinetide's potential benefits in acute ischemic stroke.

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**Conflict of Interest:** none to declare

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