Nerinetide: A Potential Neuroprotectant as Adjunct to Thrombectomy for Acute Stroke

Jean-Claude Baron

The Canadian Journal of Neurological Sciences

CAMBRIDGE UNIVERSITY PRESS

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

Journal:	*The Canadian Journal of Neurological Sciences*
Manuscript ID	Draft
Manuscript Type:	Letter to the Editor
Date Submitted by the Author:	n/a
Complete List of Authors:	baron, jean-claude; INSERM U1266,
Keywords:	STROKE, NEUROLOGY - CLINICAL, THROMBOLYSIS
Abstract:	

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

Jean-Claude Baron, MD, ScD

Dept of Neurology, Université de Paris, Groupe Hispotalier Universitaire, Hopital Sainte-Anne, Inserm U1266, Paris, France ; and

Stroke Research Group, University of Cambridge, Cambridge, UK

Word Count: 495

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[1]. 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[2]. 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[3].

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[4, 5]. 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[6], 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[2], 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[2]. In the primate study, complete recanalization was achieved in all subjects[6], as compared to ~45% of the enrolled patients in the ESCAPE-NA1 trial. Third, as supported by subgroup analysis[3], 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[7] and is considered safe and reasonable as per current American Heart Association guidelines[8], 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 neretinide. Further trials are warranted before one can confidently conclude regarding nerinetide's potential benefits in acute ischemic stroke.

Acknowledgements: none

Conflict of Interest: none to declare

1. Xie Y, Oppenheim C, Guillemin F, Gautheron V, Gory B, Raoult H, et al. Pretreatment lesional volume impacts clinical outcome and thrombectomy efficacy. *Ann Neurol*. 2018;83:178-185
2. Baron J-C. Protecting the ischaemic penumbra as an adjunct to thrombectomy for acute stroke. *Nature Reviews Neurology*. 2018;14:325-337
3. Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, et al. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (escape-na1): A multicentre, double-blind, randomised controlled trial. *Lancet*. 2020
4. Puhr-Westerheide D, Tiedt S, Rotkopf LT, Herzberg M, Reidler P, Fabritius MP, et al. Clinical and imaging parameters associated with hyperacute infarction growth in large vessel occlusion stroke. *Stroke*. 2019;50:2799-2804
5. Wheeler HM, Mlynash M, Inoue M, Tipirnini A, Liggins J, Bammer R, et al. The growth rate of early dwi lesions is highly variable and associated with penumbral salvage and clinical outcomes following endovascular reperfusion. *Int J Stroke*. 2015;10:723-729
6. Cook DJ, Teves L, Tymianski M. Treatment of stroke with a psd-95 inhibitor in the gyrencephalic primate brain. *Nature*. 2012;483:213-217
7. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med*. 2018;378:1573-1582
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2019;50:e344-e418