Nerinetide

- Impact of Brain Frailty on Clinical Presentation and Neurologic Recovery in Acute Ischemic Stroke Patients Undergoing Thrombectomy
- Comparing Early National Institutes of Health Stroke Scale Versus 90-Day Modified Rankin Scale Outcomes in Acute Ischemic Stroke Trials: A Systematic Review and Analysis
- Neuroprotective strategies in acute ischemic stroke: A narrative review of recent advances and clinical outcomes
- Safety and efficacy of nerinetide in patients with acute ischaemic stroke enrolled in the early window: a post-hoc meta-analysis of individual patient data from three randomised trials
- Efficacy and safety of nerinetide in acute ischaemic stroke in patients undergoing endovascular thrombectomy without previous thrombolysis (ESCAPE-NEXT): a multicentre, double-blind, randomised controlled trial
- Efficacy and safety of intravenous nerinetide initiated by paramedics in the field for acute cerebral ischaemia within 3 h of symptom onset (FRONTIER): a phase 2, multicentre, randomised, double-blind, placebo-controlled study
- Comparison of Noncontrast Computed Tomography, Multiphase Computed Tomography Angiography, and Computed Tomography Perfusion to Assess Infarct Growth Rate in Acute Stroke
- Factors Influencing Nerinetide Effect on Clinical Outcome in Patients Without Alteplase Treatment in the ESCAPE-NA1 Trial

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Nerinetide (also known as NA-1) is a neuroprotective drug that has been studied for its potential use in acute ischemic stroke treatment. The drug works by inhibiting the activity of a protein called PSD-95, which is involved in the death of brain cells following a stroke.

Nerinetide has been shown to reduce brain damage and improve functional outcomes in preclinical models of stroke. In Phase II clinical trial, nerinetide was found to be safe and well-tolerated and to improve functional outcomes in patients with acute ischemic stroke who received intravenous tissue plasminogen activator (tPA) therapy.

However, in a subsequent Phase III clinical trial, called the ESCAPE-NA-1 study, nerinetide did not meet its primary endpoint of reducing disability after 90 days compared to placebo in patients with acute ischemic stroke who underwent endovascular treatment. Despite this, some experts believe that nerinetide may still have potential as a neuroprotective agent for certain patient populations, and further research is ongoing.

It is important to note that nerinetide is not currently approved for use in the treatment of acute ischemic stroke, and should only be used in the context of a clinical trial or under the direction of a healthcare provider.

A cohort study was a post hoc analysis of the Safety and Efficacy of Nerinetide (NA-1) in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) randomized clinical trial, which investigated intravenous (IV) nerinetide in patients who underwent EVT within a 12-hour treatment window. Patients from 48 acute care hospitals in 8 countries (Canada, US, Germany, Korea, Australia,

Ireland, UK, and Sweden) were enrolled between March 1, 2017, and August 12, 2019. Markers of brain frailty (brain atrophy [subcortical or cortical], white matter disease [periventricular or deep], and the number of lacunes and chronic infarctions) were retrospectively assessed while reviewers were blinded to other imaging (eg, computed tomography angiography, computed tomography perfusion) or outcome variables. All analyses were done between December 1, 2022, and January 31, 2023.

Exposures: All patients received EVT and were randomized to IV nerinetide (2.6 mg/kg of body weight) and alteplase (if indicated) treatment vs best medical management.

Main outcome and measures: The primary outcome was the proportion of the total effect of age on 90-day outcome, mediated by neuroimaging frailty. A combined mediation was also examined by clinical features associated with frailty and neuroimaging markers (total frailty). Structural equation modeling was used to create latent variables as potential mediators, adjusting for baseline, early ischemic changes; stroke severity; onset-to-puncture time; nerinetide treatment; and alteplase treatment.

Results: Among a total of 1105 patients enrolled in the study, 1102 (median age, 71 years [IQR, 61-80 years]; 554 [50.3%] male) had interpretable imaging at baseline. Of these participants, 549 (49.8%) were treated with IV nerinetide. The indirect effect of age on 90-day outcome, mediated by neuroimaging frailty, was associated with 85.1% of the total effect (β coefficient, 0.04 per year [95% CI, 0.02-0.06 per year]; P < .001). When including both frailty constructs, the indirect pathway was associated with essentially 100% of the total effect (β coefficient, 0.07 per year [95% CI, 0.03-0.10 per year]; P = .001).

In this cohort study, a secondary analysis of the ESCAPE-NA1 trial, most of the association between age and 90-day outcome was mediated by neuroimaging frailty, underscoring the importance of features like brain atrophy and small vessel disease, as opposed to chronological age alone, in predicting poststroke outcomes. Future trials could include such frailty features to stratify randomization or improve adjustment in outcome analyses [1)].

Infarct in a new territory (INT) is a known complication of endovascular stroke therapy. Singh et al. assessed the incidence of INT, outcomes after INT, and the impact of concurrent treatments with intravenous thrombolysis and nerinetide.

Data are from the ESCAPE-NA1 trial (Safety and Efficacy of Nerinetide [NA-1] in Subjects Undergoing Endovascular Thrombectomy for Stroke), a multicenter, international randomized study that assessed the efficacy of intravenous nerinetide in subjects with acute ischemic stroke who underwent endovascular thrombectomy within 12 hours from onset. Concurrent treatment and outcomes were collected as part of the trial protocol. INTs were identified on core lab imaging review of follow-up brain imaging and defined by the presence of infarct in a new vascular territory, outside the baseline target occlusion(s) on follow-up brain imaging (computed tomography or magnetic resonance imaging). INTs were classified by maximum diameter (<2, 2-20, and >20 mm), number, and location. The association between INT and clinical outcomes (modified Rankin Scale and death) was assessed using standard descriptive techniques and adjusted estimates of effect were derived from Poisson regression models.

Among 1092 patients, 103 had INT (9.3%, median age 69.5 years, 49.5% females). There were no differences in baseline characteristics between those with and without INT. Most INTs (91/103, 88.3%) were not associated with visible occlusions on angiography and 39 out of 103 (37.8%) were >20 mm in maximal diameter. The most common INT territory was the anterior cerebral artery (27.8%). Almost

half of the INTs were multiple (46 subjects, 43.5%, range, 2-12). INT was associated with poorer outcomes as compared to no INT on the primary outcome of the modified Rankin Scale score of 0 to 2 at 90 days (adjusted risk ratio, 0.71 [95% CI, 0.57-0.89]). Infarct volume in those with INT was greater by a median of 21 cc compared with those without, and there was a greater risk of death as compared to patients with no INT(adjusted risk ratio, 2.15 [95% CI, 1.48-3.13]).

Infarcts in a new territory are common in individuals undergoing endovascular thrombectomy for acute ischemic stroke and are associated with poorer outcomes. Optimal therapeutic approaches, including technical strategies, to reduce INT represent a new target for incremental quality improvement of endovascular thrombectomy [2].

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Benali F, Singh N, Fladt J, Jaroenngarmsamer T, Bala F, Ospel JM, Buck BH, Dowlatshahi D, Field TS, Hanel RA, Peeling L, Tymianski M, Hill MD, Goyal M, Ganesh A; ESCAPE-NA1 Investigators. Mediation of Age and Thrombectomy Outcome by Neuroimaging Markers of Frailty in Patients With Stroke. JAMA Netw Open. 2024 Jan 2;7(1):e2349628. doi: 10.1001/jamanetworkopen.2023.49628. PMID: 38165676.
2)
Singh N, Cimflova P, Ospel JM, Kashani N, Marko M, Mayank A, Nogueira RG, McTaggart RA, Demchuk AM, Poppe AY, Rempel JL, Field TS, Dowlatshahi D, van Adel B, Swartz RH, Shah R, Sauvageau E, Puetz V, Silver FL, Campbell B, Chapot R, Tymianski M, Goyal M, Almekhlafi MA, Hill MD; ESCAPE-NA1 Trial Investigators. Infarcts in a New Territory: Insights From the ESCAPE-NA1 Trial. Stroke. 2023 Apr 21. doi: 10.1161/STROKEAHA.122.042200. Epub ahead of print. PMID: 37082967.