

Hope Dies Last—Evidence Again Fails to Support a Neuroprotectant Cerebrolysin for Acute Ischemic Stroke

Daniel Berezki, MD, DSc, FESO

See related article, p e245

It has been a long-lasting hope in basic and clinical research to identify neuroprotectant agents that improve clinical outcome after an ischemic stroke. Over a thousand compounds have been tested in the western world¹ without identifying a single compound supported by firm evidence for use in acute stroke. Although 21 traditional Chinese medicines evaluated in clinical trials claimed to improve clinical outcome after stroke and 7 of them also allegedly decreased case fatality,² because of methodological flaws in these trials, no recommendations can be made on these treatments until properly designed trials are completed.³ None of the Cochrane reviews recommends the use of any neuroprotectants for the treatment of acute stroke,⁴ and current guidelines are also against the use of such agents.⁵

Cerebrolysin is an extract of porcine brain containing a mixture of free amino acids and oligopeptides.⁶ Randomized clinical trials addressed its safety and efficacy in several conditions like Alzheimer's disease⁷ and traumatic brain injury.⁸ One recent Cochrane review based on 6 trials evaluates the effects of cerebrolysin in acute ischemic stroke and concludes that the use of cerebrolysin has no effect on fatality.^{9,10} Five of the included trials were small, and in the largest trial, the comparison groups were not balanced for prognostic factors. The loss to follow-up was considerable in the trials. None of the 6 trials, including overall 1501 participants, had low risk of bias.

The predefined primary outcome is one of the most important issues in clinical trials. Death is certainly an important outcome, but dependency on others is also a bad outcome after stroke. Death or dependency, the preferred composite primary outcome after stroke, was not a primary outcome in any of the 6 trials. Although subgroup and post hoc analyses suggested potential benefit, the largest study with over 1000 patients¹¹ had neutral results regarding the predefined primary outcome: a combined test of the modified Rankin Scale, the Barthel Index, and the National Institutes of Health Stroke Scale at the end of follow-up. No significant effect on neurological signs or disability was reported in 2 smaller

trials with over 100 participants.^{12,13} The rest 3 trials included <50 patients each.

Despite the lack of evidence from systematic reviews for efficacy regarding both fatality⁹ and functional outcome,¹⁴ cerebrolysin has been used in several countries, with limited healthcare resources in Asia and Eastern Europe. Although subgroup- and post hoc analyses suggested potential benefit of cerebrolysin, these claims should be currently considered only hypotheses. The routine use of cerebrolysin in acute stroke is not justified until randomized well-designed trials indeed prove efficacy in these patient groups. In these trials, patient-centered predefined outcomes will have to be used.¹⁵

Disclosures

None.

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From the Department of Neurology, Semmelweis University, Budapest, Hungary.

Correspondence to Daniel Berezki, DSc, FESO, Department of Neurology, Semmelweis University, Budapest, Balassa u. 6., H-1083, Hungary. E-mail berezki@neur.sote.hu

(*Stroke*. 2017;48:2343–2344.)

DOI: 10.1161/STROKEAHA.117.018202.)

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.117.018202

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KEY WORDS: Editorials ■ effectiveness ■ neuroprotectant ■ outcome
■ stroke ■ systematic review

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Daniel Berezcki

Stroke. 2017;48:2343-2344; originally published online July 26, 2017;
doi: 10.1161/STROKEAHA.117.018202

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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