

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

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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.

References

- O'Collins VE, Macleod MR, Donnan GA, Horkey LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Ann Neurol*. 2006;59:467–477. doi: 10.1002/ana.20741.
- Wu B, Liu M, Liu H, Li W, Tan S, Zhang S, et al. Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke*. 2007;38:1973–1979. doi: 10.1161/STROKEAHA.106.473165.
- Berezki D. The seven wonders of China in stroke therapy: fact or illusion? *Stroke*. 2007;38:e142; author reply e143. doi: 10.1161/STROKEAHA.107.495515.
- The Cochrane Library. <http://www.cochranelibrary.com>. Accessed June 22, 2017.
- Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. doi: 10.1161/STR.0b013e318284056a.
- Kofler B, Erhart C, Erhart P, Harrer G. A multidimensional approach in testing nootropic drug effects (Cerebrolysin). *Arch Gerontol Geriatr*. 1990;10:129–140.
- Alvarez XA, Cacabelos R, Sampedro C, Couceiro V, Aleixandre M, Vargas M, et al. Combination treatment in Alzheimer's disease: results of a randomized, controlled trial with cerebrolysin and donepezil. *Curr Alzheimer Res*. 2011;8:583–591.
- Chen CC, Wei ST, Tsaia SC, Chen XX, Cho DY. Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients: double-blind, placebo-controlled, randomized study. *Br J Neurosurg*. 2013;27:803–807. doi: 10.3109/02688697.2013.793287.
- Ziganshina LE, Abakumova T, Vernay L. Cerebrolysin for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2017;4:CD007026. doi: 10.1002/14651858.CD007026.pub5.
- Ziganshina LE, Abakumova T, Vernay L. Cerebrolysin for acute ischemic stroke. *Stroke*. 2017;48:e245–e246. doi: 10.1161/STROKEAHA.117.017841.
- Heiss WD, Brainin M, Bornstein NM, Tuomilehto J, Hong Z; Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke*. 2012;43:630–636. doi: 10.1161/STROKEAHA.111.628537.
- Lang W, Stadler CH, Poljakovic Z, Fleet D; Lyse Study Group. A prospective, randomized, placebo-controlled, double-blind trial about safety and

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- efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke. *Int J Stroke*. 2013;8:95–104. doi: 10.1111/j.1747-4949.2012.00901.x.
13. Ladurner G, Kalvach P, Moessler H; Cerebrolysin Study Group. Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial. *J Neural Transm (Vienna)*. 2005;112:415–428. doi: 10.1007/s00702-004-0248-2.
 14. Wang Z, Shi L, Xu S, Zhang J. Cerebrolysin for functional recovery in patients with acute ischemic stroke: a meta-analysis of randomized controlled trials. *Drug Des Devel Ther*. 2017;11:1273–1282. doi: 10.2147/DDDT.S124273.
 15. Salinas J, Sprinkhuizen SM, Ackerson T, Bernhardt J, Davie C, George MG, et al. An International standard set of patient-centered outcome measures after stroke. *Stroke*. 2016;47:180–186. doi: 10.1161/STROKEAHA.115.010898.

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