Cerebrolysin for vascular dementia (Review)

Ning Chen[1], Mi Yang[1], Jian Guo[1], Muke Zhou[1], Cairong Zhu[2], Li He[1]

[1]Department of Neurology, West China Hospital, Sichuan University, Chengdu, China; [2]Epidemic Disease & Health Statistics Department, School of Public Health, Sichuan University, Sichuan, China

Address for correspondence to Li He: Department of Neurology, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan, 610041, China, heli2003new@126.com

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Introduction

Vascular dementia is a common disorder without definitive treatments. Cerebrolysin is reported to be effective in treatment of VaD in some clinical trials, but there is no compelling evidence. So, to guide clinical practice and studies, it is necessary to systematically review the efficacy and safety.

Methods

We searched ALOIS – the Cochrane Dementia and Cognitive Improvement Group's Specialized Register using the terms: Cerebrolysin, Cere, FPF1070, and FPF-1070. ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases, numerous trial registries and grey literature sources. All randomized controlled trials of Cerebrolysin for treating vascular dementia without language restriction were retrieved for analysis. Two authors independently selected trials and evaluated the methodological quality, then extracted and analyzed data from the included trials. We identified six trials involving 597 participants suitable for inclusion in this review (Fig.1-2).

Fig. 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

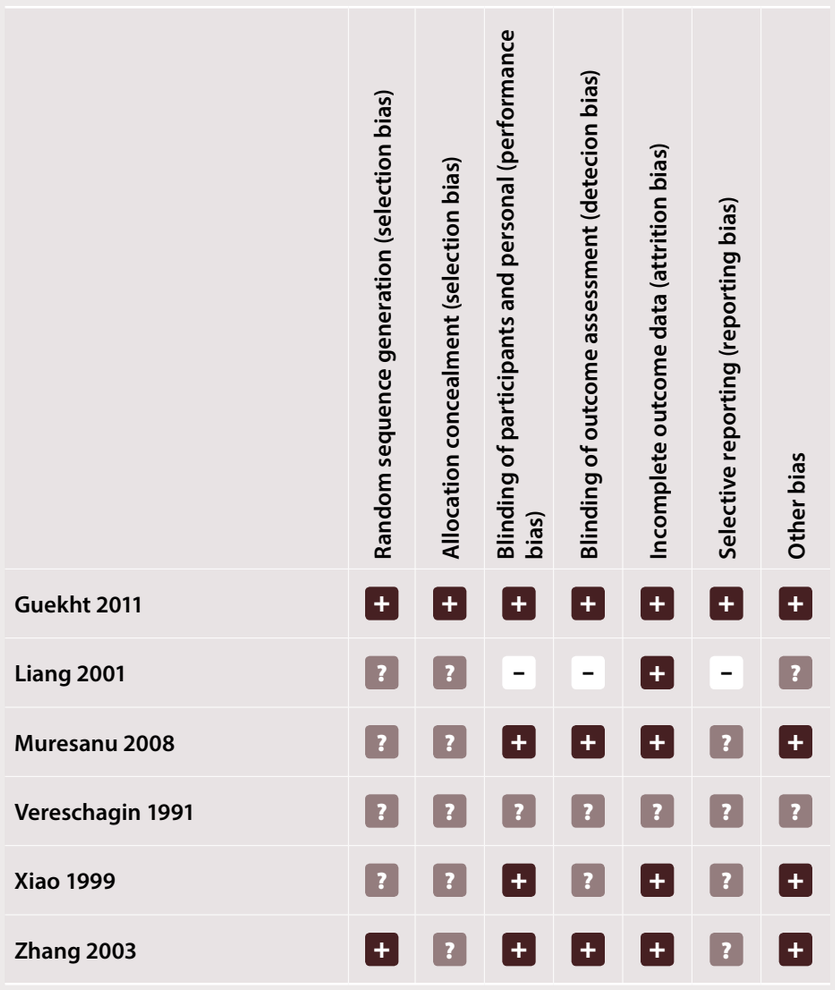


Fig. 2. Clinical trials of Cerebrolysin in VaD included in the Cochrane review

Trials	N Cere /placebo	Arms	Treatments/ duration	Dose	Main outcomes
Xiao et al., 1999 DB, R	147 (75/72)	Cere 0.9% NaCl	4 weeks/ 4 weeks	30 mL	MMSE, CGI, HamD, SCAG, NAI, ADL, TMT
Guekht et al., 2011 DB, R	242 (121/121)	Cere 0.9% NaCl	2x4 weeks/ 24 weeks	20 mL	ADAS-cog+, CIBIC+, CIBIS+, MMSE, ADCS-ADL, TMT A, Clock drawing
Muresanu et al., 2008 DB, R	41 (31/10) (10 mL: 16; 30 mL: 15)	Cere 0.9% NaCl	4 weeks/ 4 weeks (only DB)	10/30 mL	MMSE, ADAS-cog+, qEEG
Zhang 2003 DB, R	29	Cere + Xuesaitong 0.9% NaCl+ Xuesaitong	10 days X 6/ 3 years	20 mL	MMSE, WISA-RC
Liang 2001 Non-bling, R	77	Cere 0.9% NaCl	15 days/ 15 days	20 mL	HDS
Vereschagin 1991 DB, R	60 (30/30)	Cere 0.9% NaCl	4 weeks/ 4 weeks	15+5 mL	Clinical evaluations (special scale), EEG, Arnold-Kohlmann psychological test for response time

MMSE: Mini-Mental State Examination; ADL – activities of daily living; Cere: Cerebrolysin; ADAS-cog+: Alzheimer's Disease Assessment Scale Cognitive Subpart, Extended Version; CIBIC+: Clinician's Interview-Based Impression of Change plus Caregiver Input; NAI – neurological assessment instrument; CGI – clinical global impression; CIBIS+: Clinician's Interview-Based Impression of Severity; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; HDS: Hasegawa Dementia Scale; qEEG: quantitative electroencephalogram; TMT – trail making test; GDS: Global Deterioration Scale; WISA-RC: Wechsler Intelligence Scale for Adult – Revised for Chinese; NaCl: sodium chloride; DB – double blind; R – recombinant.

Meta-analyses of the studies reporting on the efficacy of Cerebrolysin for VaD were performed, in which the results were displayed as a forest plot. Only trials that provided a measure of effect size were included. Descriptive analyses of other included trials were also undertaken. The methodology of the meta-analysis has been conducted according to Cochrane Collaboration standards (see original publication).

Results

The meta-analyses revealed a beneficial effect of Cerebrolysin on general cognitive function measured by mini-mental state examination (MMSE) (weighted mean difference (WMD) 1.10; 95% confidence interval (CI) 0.37 to 1.82) or Alzheimer's Disease Assessment Scale Cognitive Subpart, extended version (ADAS-cog+) (WMD -4.01; 95% CI -5.36 to -2.66). The major results are summarized on Fig. 3-5.

Fig. 3. Forest plot of comparison: Cognitive function, outcome: The change of general cognitive function measured by MMSE

	Cerebrolysin			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Guekht 2011	4.653	5.7	117	3.168	5.405	115	25.9%	1.48 [0.06, 2.91]	
Xiao 1999	2.68	2.61	75	1.72	2.61	72	74.1%	0.96 [0.12, 1.80]	
Total (95% CI)			**192**			**187**	**100.0%**	**1.10 [0.37, 1.82]**	

Heterogeneity: Chi^2=0.38, df=1 (P=0.54); I^2=0%
Test for overall effect: Z=2.96 (P=0.003)

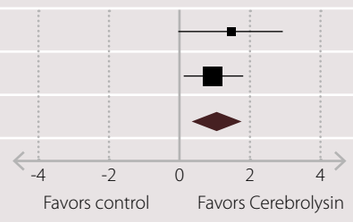


Fig. 4. Forest plot of comparison: Cognitive function, outcome: The change of general cognitive function measured by ADAS-cog+ score

	Cerebrolysin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Guekht 2011	-10.6	7.77	117	-4.49	8.13	115	43.7%	-6.11 [-8.16, -4.06]	
Muresanu 2008	-2.41	2.71	31	-0.03	2.47	10	56.3%	-2.38 [-4.18. -0.58]	
Total (95% CI)			**148**			**125**	**100.0%**	**-4.01 [-5.36, -2.66]**	

Heterogeneity: Chi^2=7.18, df=1 (P=0.007); I^2=86%
Test for overall effect: Z=5.81 (P=0.00001)

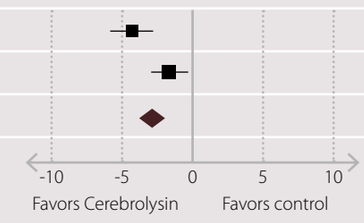
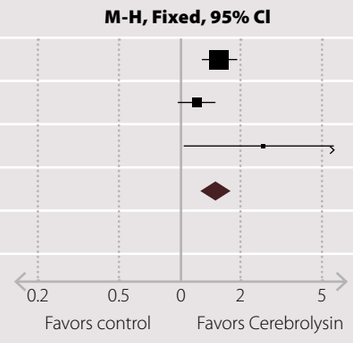


Fig. 5. Forest plot of comparison: Cognitive function, outcome: The improvement of general cognitive function reported as responder rates

	Cerebrolysin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Guekht 2011	96	117	60	115	64.6%	1.57 [1.29, 1.91]	
Liang 2001	37	40	28	37	31.0%	1.22 [1.00, 1.50]	
Zhang 2003	11	15	4	14	4.4%	2.57 [1.06, 6.20]	
Total (95% CI)		**172**		**166**	**100.0%**	**1.51 [1.30, 1.75]**	
Total events	**144**		**92**				

Heterogeneity: Chi^2=5.69, df=2 (P=0.06); I^2=65%
Test for overall effect: Z=5.40 (P=0.00001)

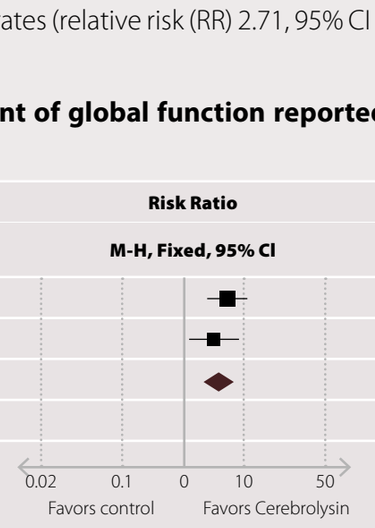


Cerebrolysin also improved patients' global clinical function evaluated by the response rates (relative risk (RR) 2.71, 95% CI 1.83 to 4.00). The major results are summarized on Fig. 6.

Fig. 6. Forest plot of comparison: Global function, outcome: The improvement of global function reported as responder rates

	Cerebrolysin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Guekht 2011	50	117	16	115	59.0%	3.07 [1.86, 5.07]	
Xiao 1999	25	75	11	72	41.0%	2.18 [1.16, 4.10]	
Total (95% CI)		**192**		**187**	**100.0%**	**2.71 [1.83, 4.00]**	
Total events	**75**		**27**				

Heterogeneity: Chi^2=0.69, df=1 (P=0.41); I^2=0%
Test for overall effect: Z=4.99 (P=0.00001)



Only non-serious adverse events were observed in the included trials, and there was no significant difference in occurrence of non-serious side effects between groups (RR 0.97, 95% CI 0.49 to 1.94). Major results are presented on Fig. 7.

Fig. 7. Forest plot of comparison: Adverse events, outcome: Non-serious adverse events

	Cerebrolysin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Guekht 2011	11	117	7	115	46.4%	1.54 [0.62, 3.84]	
Xiao 1999	4	75	8	72	53.6%	0.48 [0.15, 1.52]	
Total (95% CI)		**192**		**187**	**100.0%**	**0.97 [0.49, 1.94]**	
Total events	**15**		**15**				

Heterogeneity: Chi^2=2.42, df=1 (P=0.12); I^2=59%
Test for overall effect: Z=0.08 (P=0.94)

Conclusion

Cerebrolysin may have positive effects on the improvement of cognitive function and global function in older patients with VaD of mild to moderate severity. Most side effects related to Cerebrolysin are rated as mild to moderate in severity. However, due to the limited number of included trials, variable treatment duration and short-term follow-up, there is insufficient evidence to recommend Cerebrolysin as a routine treatment for patients with VaD. Further, it is difficult for it to be used widely since this medicine must be given by intravenous infusion with a long-term, demanding treatment schedule.

Related references

1. Original article: The Cochrane Collaboration; published in The Cochrane Library 2013, Issue 1
2. POSTER: Gauthier S et al., 2014. Cerebrolysin in mild to moderate Alzheimer's disease: A meta-analysis of randomized controlled clinical trials