Cerebrolysin for vascular dementia (Review)

Chen N, Yang M, Guo J, Zhou M, Zhu C, He L

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[Intervention Review]

Cerebrolysin for vascular dementia

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ABSTRACT

Background

Vascular dementia is a common disorder without definitive treatments. Cerebrolysin seems to be a promising intervention based on its potential neurotrophic and pro-cognitive effects, but studies of its efficacy have yielded inconsistent results.

Objectives

To assess the efficacy and safety of Cerebrolysin for vascular dementia.

Search methods

We searched ALOIS - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 4 November 2012 using the terms: Cerebrolysin, Cere, FPF1070, 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.

Selection criteria

All randomized controlled trials of Cerebrolysin for treating vascular dementia without language restriction.

Data collection and analysis

Two authors independently selected trials and evaluated the methodological quality, then extracted and analysed data from the included trials.

Main results

Six randomized controlled trials with a total of 597 participants were eligible. 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). It also improved patients' global clinical function evaluated by the response rates (relative risk (RR) 2.71, 95% CI 1.83 to 4.00). 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).

Authors' conclusions

Cerebrolysin may have positive effects on cognitive function and global function in elderly patients with vascular dementia of mild to moderate severity, but there is still insufficient evidence to recommend Cerebrolysin as a routine treatment for vascular dementia due to the limited number of included trials, wide variety of treatment durations and short-term follow-up in most of the trials.

PLAIN LANGUAGE SUMMARY

Cerebrolysin for vascular dementia

Vascular dementia (VaD) is a common disorder which currently lacks definitive treatments. Cerebrolysin, a peptide preparation produced from purified pig brain proteins, seems to be a promising intervention based on animal studies and clinical trials in other conditions. We identified six trials involving 597 participants suitable for inclusion in this review. Pooled results showed improvements in cognitive function and global function in patients with VaD of mild to moderate severity, with no obvious side effects related to Cerebrolysin. However, due to the limited number of included trials, varying treatment durations and short-term follow-up, there is insufficient evidence to recommend Cerebrolysin as a routine treatment for patients with VaD.

BACKGROUND

Description of the condition

Vascular dementia (VaD) is a common disorder among the elderly, which can also occur in younger people. Incidence data vary considerably: it is the second most common form of dementia after Alzheimer's disease (AD) in the western world (Neuropathology Group 2001) and in China (Dong 2007; Zhang 2012), while it is deemed the most common cause of dementia in Japan (Aggarwal 2007). The differences may be due in part to different study methodologies and diagnostic criteria. Rates of both major types of dementia increase with age; it has been estimated that the prevalence rate of VaD doubles every 5.3 years compared with every 4.5 years for AD (O'Brien 2003).

The term vascular dementia refers to a constellation of cognitive and functional impairments. It can be viewed as a subset of the larger syndrome of vascular cognitive impairment (VCI) associated with cerebrovascular brain injury (Aggarwal 2007). As an etiologic category, VaD includes dementia caused by ischemic or hemorrhagic cerebrovascular disease (CVD) or by ischemic-hypoxic brain lesions of cardiovascular origin (Román 2002). The following has been proposed as a classification of the subtypes of VaD (O'Brien 2006):

(i) multi-infarct dementia (cortical VaD); (ii) small-vessel dementia (subcortical VaD); (iii) strategic infarct dementia; (iv) hypoperfusion dementia; (v) hemorrhagic dementia; (vi) AD with cerebrovascular disease (CVD); (vii) hereditary vascular dementia (CADASIL).

Although this classification is based on clinical differences and underlying pathologic changes, it is difficult to classify a patient into one definite subtype in many cases, because these subtypes are usually not pure and mixtures of pathology frequently combine to contribute to cognitive impairment (Moorhouse 2008).

There are several diagnostic criteria for VaD, such as Diagnostic and Statistical Manual of Mental Disorders, third, third revised, fourth edition (DSM-III, DSM III-R, DSM-IV) (APA 1980; APA 1987; APA 1994), Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria (Chui 1992), International Statistical Classification of Diseases, 10th revision (ICD 10) (WHO 1992), and National Institute of Neurological Disorders and Stroke Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Román 1993). All of these criteria are based on two major requirements: clinical diagnosis of dementia and determination of its vascular origin. The latter requirement is problematic because of the frequent overlap between cerebrovascular and degenerative disorders, particularly in the elderly (Benisty 2008). As a result, the current diagnostic criteria for VaD are not concordant, which may make data analysis and comparisons difficult (Moorhouse 2008). A wide range of instruments has been used in the assessment of cognitive function in patients with VaD. However, since the most typical expression of VaD is executive dysfunction, the widely used mini-mental state examination (MMSE) may underestimate the cognitive decline in patients with VaD, because it contains few items related to executive functions (Folstein 1975; Moorhouse 2008). The Montreal Cognitive Assessment (MoCA) may be more appropriate in such cases (Nasreddine 2005; Korczyn 2012).

There are currently no definitive treatments for VaD. Interventions are possible at a number of levels: primary prevention, secondary prevention, symptomatic treatments and disease modifying or curative approaches (O'Brien 2006). Available data on the treatment of vascular risk factors show surprisingly equivocal support for their value in primary and secondary prevention (Moorhouse 2008). Such strategies are undoubtedly beneficial in preventing stroke or stroke recurrence, which contributes importantly to global cognitive decline (Srikanth 2006). However, a meta-analysis (Feigin 2005) and a Cochrane systematic review (McGuinness 2009) of randomized controlled trials of antihypertensives found, respectively, a non-significant trend and no convincing evidence that lowering blood pressure prevented cognitive decline and dementia. Potential symptomatic treatment for VaD, such as vasodilators, nosotropics, antioxidants (O'Brien 2006; Moorhouse 2008) and some traditional Chinese herbal medicines (Wu 2007; Hao 2009), have been evaluated in multiple trials and systematic reviews, but agents with proven effects and safety are still lacking. The effects of drugs used to treat AD are modest in patients with VaD (Moorhouse 2008): a meta-analysis concluded that cholinesterase inhibitors and memantine provided only small benefits of uncertain clinical significance (Kavirajan 2007).

Description of the intervention

Cerebrolysin is a peptide preparation, produced from purified pig brain proteins by standardized enzymatic breakdown. It is a mixture of 80% low-molecular-weight peptides and 20% free amino acids, with potential neurotrophic and neuroprotective activity (Windisch 1998; Álvarez 2006). Cerebrolysin is supplied as a solution for injection or infusion, and it is recommended to be given as intravenous infusion (10 ml - up to 30 ml Cerebrolysin for severe cases, diluted in physiologic saline or glucose injection) once daily for appropriate patients with dementia. Five days a week repeated for four weeks is one cycle, and two to four treatment cycles might be repeated per year (www.ebewe-neuro.com; Plosker 2009).
Cerebrolysin has been reported to improve clinical global impression, cognitive performance and the performance of activities of daily living in patients with stroke (Hong 2005; Ladurner 2005), AD (Álvarez 2006) and traumatic brain injury (Álvarez 2003). In a multicenter randomized double-blind placebo-controlled study conducted in Austria, a total of 146 patients with acute ischemic stroke received 50 ml Cerebrolysin or placebo intravenously daily for 21 days. Patients taking Cerebrolysin showed significant benefit on cognitive function but not neurological scores (Ladurner 2005). The Cochrane systematic review evaluating efficacy of Cerebrolysin for acute ischemic stroke only included the above study, and concluded that there was not enough evidence to evaluate the effect of Cerebrolysin for those patients (Ziganshina 2010). Another large randomized double-blind placebo-controlled study with 279 patients in Spain investigated the efficacy and safety of three dosages of Cerebrolysin for AD. Patients received intravenous infusions of 10 ml, 30 ml and 60 ml Cerebrolysin or placebo five days per week for four weeks and then two infusions per week for eight weeks. In this study, Cerebrolysin led to significant and dose-dependent improvement of cognition and global clinical impression (Álvarez 2006). The Cochrane systematic review of Cerebrolysin for AD (Fragoso 2009) is still in progress currently.

How the intervention might work

Cerebrolysin has neurotrophic activity demonstrated in various models *in vitro* and *in vivo*. For example, it exerts nerve growth factor (NGF)-like activity on neurons from dorsal root ganglia (Satou 1993). Its multiple effects include promotion of neuroprotection, neuroplasticity and neurogenesis. Several in vitro and in vivo studies suggest possible mechanisms for these actions:
(1) Cerebrolysin may reduce amyloid plaque formation by regulating amyloid precursor protein (APP) (Rockenstein 2006).
(2) It may protect neurons from apoptosis and degeneration, probably through the inhibition of calpain (Akai 1992; Hartbauer 2001).
(3) It may modulate neuronal connectivity by increasing neuritic outgrowth, protecting established neurites against degeneration and increasing synaptic density, thereby supporting neuroplastic processes (Masliah 1999; Rockenstein 2003).
(4) It may also reduce the physiological apoptosis of newborn cells and increase the number of new neurons, thus stimulating neurogenesis (Tatebayashi 2003).
Various animal models have been established to demonstrate the neurotrophic and pro-cognitive effects of Cerebrolysin (Veinbergs 2000; Rockenstein 2005).

Why it is important to do this review

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.

OBJECTIVES

To assess the efficacy and safety of Cerebrolysin for vascular dementia.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomized controlled trials (RCTs), blinded or unblinded, were eligible for inclusion irrespective of any language restrictions.

Types of participants

Participants of all ages and both sexes with a diagnosis of vascular dementia. The diagnoses were made using accepted, validated criteria, e.g. DSM-III, DSM III-R, DSM-IV, ADDTC, ICD10, NINDS-AIREN. Studies involving only a subset of participants with VaD were also included, if the data of relevant patients could be extracted.

Types of interventions

Cerebrolysin at any dose and for any length of treatment period versus control interventions.
The following treatment comparisons were investigated:
(1) Cerebrolysin alone compared with placebo.
(2) Cerebrolysin alone compared with no treatment.
(3) Cerebrolysin plus another treatment compared with placebo plus the same other treatment.
(4) Cerebrolysin plus another treatment compared with the same other treatment alone.

Types of outcome measures

All outcomes included in the analysis of the current review were measured with a validated scale.

Primary outcomes

(1) Cognitive function.
(2) Global function.
(3) All cause death.

Secondary outcomes

(1) Adverse events.
(2) Quality of life.
(3) Carer burden.

Search methods for identification of studies

We searched for all RCTs of Cerebrolysin for vascular dementia, irrespective of any language restrictions.

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 4 November 2012. The search terms used were: Cerebrolysin, Cere, FPF1070, FPF-1070.
ALOIS is maintained by the Trials Search Co-ordinator for the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy persons. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
3. quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.
Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.
Additional searches were performed in many of the sources listed above to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.
The search (November 2012) retrieved a total of 96 results. After a first-assess and a de-duplication of these results the authors were left with 25 references to further assess.

Searching other resources

We checked the references of published studies to identify additional trials. We also reviewed the bibliographies of the trials identified, contacted the authors and known experts in the field to identify additional published or unpublished data. We approached the medical information department of the relevant companies with a request for copies of all conference posters which described clinical studies with Cerebrolysin as well.

Data collection and analysis

Selection of studies

Two review authors (N Chen and M Yang) independently scrutinized titles and abstracts identified from the register. The two authors obtained the full text of all potentially relevant studies for independent assessment, and then decided which trials fitted the inclusion criteria. When there were disagreements about inclusion criteria, the two authors discussed the discrepancy carefully. A third review author (L He) helped to arbitrate if there was a failure in resolving disagreement.

Data extraction and management

Two authors (N Chen and M Yang) independently extracted data from the trials to fill in a data extraction form. It included the study name, type of design, study population size, duration, number of participant withdrawals, participants analysed in the different treatment groups, inclusion and exclusion criteria, intervention (route and dosage), and outcomes. One author (N Chen) entered data into Review Manager (RevMan 5) and a second author (M Yang) checked the data entry.

Assessment of risk of bias in included studies

The assessment of risk of bias took into account the security of randomization, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and any other potential sources of bias. These items were assessed by two authors (N Chen and M Yang) independently according to the Cochrane risk of bias tool (Higgins 2011b). Then all trials were judged for each item and subdivided into the following three categories:

A. Low risk of bias for all key domains: low risk of bias.

B. Unclear risk of bias for one or more key domains: unclear risk of bias.

C. High risk of bias for one or more key domains: high risk of bias.

Measures of treatment effect

We analyzed the data using Cochrane RevMan 5 software. A weighted treatment effect was calculated using a fixed-effect model across trials unless there was substantial heterogeneity, in which case a random-effects approach was used. Results were expressed as relative risks (RRs) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes, both with 95% confidence intervals (CIs). If the differences in effect with the standard error were available, but the standard deviations of the individual study groups were not, we used the RevMan Generic Inverse Variance (GIV) facility to pool studies.

Unit of analysis issues

In order to avoid unit-of-analysis errors resulting from combining results from more than one time point for each study in a standard meta-analysis, we used final time-point data from each trial, and analysed subgroups based on treatment duration in the presence of any evidence of heterogeneity (Deeks 2011). For studies that compared more than two groups, we selected the pair of groups relevant to the review questions or combined intervention groups to include in the analyses.

Dealing with missing data

We tried to obtain missing data from the study authors whenever possible. We analysed data on an intention-to-treat (ITT) basis, then all participants with available data were included in the analysis in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity

We assessed heterogeneity amongst trials by using the Chi^2 test with a 10% level of statistical significance ($P < 0.1$) and $I^2 > 50\%$ (Higgins 2002; Higgins 2003). If significant heterogeneity was present, we performed a cause analysis, and then undertook subgroup and sensitivity analyses. If there was still unexplained heterogeneity, the study results were combined using a random-effects model. For trials that were clinically heterogeneous or presented insufficient information for pooling, a descriptive analysis was performed (Higgins 2011a).

Assessment of reporting biases

We planned to use a funnel plot to investigate the possibility of publication bias if necessary, and then to evaluate and express the possible reporting biases. In the current review, tests for funnel plot asymmetry were not used because there were less than 10 studies included in each meta-analysis, when the power of the tests would be too low to distinguish chance from real asymmetry (Sterne 2011).

Data synthesis

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.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses to explore potential sources of heterogeneity if possible, including: ages, type and severity of VaD, drug dosage and route of administration and duration of treatment.

Sensitivity analysis

We also undertook a sensitivity analysis on the basis of methodological quality by repeating the calculation after omitting the trials with low scores on individual quality items.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
See Tables: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

A total of 21 potentially eligible trials were identified by scrutinising the titles and abstracts. We excluded 15 trials after we had screened their full text. As a result six trials fulfilled the inclusion criteria.

Included studies

Six trials (Vereschagin 1991; Xiao 1999; Liang 2001; Zhang 2003; Muresanu 2008; Guekht 2011) with a total of 597 participants were included in the present review after using the methods for selecting studies described in the Cochrane *Handbook for Systematic Reviews of Interventions* (Higgins 2011a).
Of the six included trials, two were conducted in multiple centers in the Russian Federation (Guekht 2011) and China (Xiao 1999), respectively, while the others were in a single center. Sample sizes differed between trials, ranging from 29 to 242 participants (the above two multicenter studies had more than 100 patients). The demographic characteristics were not significantly different between groups in each trial. Inclusion and exclusion criteria were explicitly stated in all studies, except the Vereschagin trial (Vereschagin 1991), which was only published in abstract form. Despite our attempts we could not obtain full details of this trial. Of the remaining five trials, two recruited patients with a confirmed diagnosis of VaD (both probable and possible VaD, Guekht 2011) or probable VaD (Muresanu 2008) according to the NINDS-AIREN criteria (Román 1993), two (Xiao 1999; Zhang 2003) enrolled VaD patients using the DSM-IV criteria (APA 1994), and the other one included patients with multi-infarct dementia based on the DSM-IIIR (APA 1987) and ICD-10 (WHO 1992) criteria. To confirm the VaD diagnosis, computed tomography (CT) or magnetic resonance imaging (MRI) scan of brain, or both, were used in all the five trials, and a Hachinski Ischemic Score (HIS, Hachinski 1975) of ≥ 7 or a modified HIS (Pantoni 1993) of > 4 was included in all the inclusion criteria as well. The severity of dementia on entry was required to be mild to moderate in four trials judged by either MMSE (Xiao 1999; Muresanu 2008; Guekht 2011) or CDR (Clinical Dementia Rating) scores (Zhang 2003), but the range of MMSE scores was not uniform (10 to 24 in Guekht 2011, 9 to 26 in Muresanu 2008, and 15 to 25 in Xiao 1999, respectively); the remaining two trials did not report the severity of VaD. The mean age of participants in each study group ranged from 60.4 to 70.8 years, indicating that most of them were old males or postmenopausal females, although this requirement was specified in only three included trials (Xiao 1999; Muresanu 2008; Guekht 2011). Mean duration of dementia was between 4.6 months and 4.3 years in three trials (Liang 2001; Zhang 2003; Muresanu 2008), and no relevant information was available from the other three trials. Common exclusion criteria across four trials (Xiao 1999; Zhang 2003; Muresanu 2008; Guekht 2011) included: patients with significant concomitant neurological or psychiatric disorders, any significant systemic illness or unstable medical condition, and patients who had recently received other drugs that might impact on cognitive function. Relevant information of patients' exclusion were not available in the other two trials (Vereschagin 1991; Liang 2001).
In all the included trials, Cerebrolysin was administered as an intravenous infusion, diluted in physiologic saline or glucose injection. Four trials compared Cerebrolysin with placebo (Vereschagin 1991; Xiao 1999; Muresanu 2008; Guekht 2011), while the other two trials compared Cerebrolysin plus routine treatment for cerebrovascular disease with the same routine treatment only (Liang 2001; Zhang 2003). The dose of Cerebrolysin used in those trials ranged from 10 ml to 30 ml daily, but the length of treatment period varied between trials. Three studies gave the intervention five days a week and repeated for four continuous weeks as one cycle -- two of them treated patients for one cycle only (Xiao 1999; Muresanu 2008), while one repeated two cycles with an interval of eight weeks (Guekht 2011). Two trials administered such medicine continuously for 15 days (Liang 2001) and 28 days (Vereschagin 1991), respectively. The remaining trial (Zhang 2003) took the longest period of treatment with Cerebrolysin, i.e. 10 days a cycle repeated for two cycles per year, and all patients were treated for a period of three years. Only one study had three comparison arms (Cerebrolysin 10 ml versus 30 ml versus physiologic saline) (Muresanu 2008).
The duration of follow-up varied considerably from 15 days to 3 years after enrolment. Losses to follow-up and withdrawals were all reported in the six trials; none was lost in the entire course of three trials (Vereschagin 1991; Liang 2001; Zhang 2003) and in the pilot phase of one study (Muresanu 2008; Muresanu 2008a). Only one trial (Guekht 2011) performed an intention-to-treat (ITT) analysis based on the last observation carried forward (LOCF) method. The most common outcome was the change of cognitive function from baseline to post-treatment evaluation, but the efficacy parameters were different between trials, including MMSE

score, ADAS-cog+ (Alzheimer's Disease Assessment Scale Cognitive Subpart, Extended Version) score, HDS (Hasegawa Dementia Scale), WISA (Wechsler Intelligence Scale for Adult), Trail-Making Test A and Clock-Drawing Test. The global function of patients before and after treatment was also reported in three studies (Vereschagin 1991; Xiao 1999; Guekht 2011), evaluated by the following measures either separately or in combination: CIBIC+ (Clinician's Interview-Based Impression of Change plus Caregiver Input), CIBIS+ (Clinician's Interview-Based Impression of Severity), ADL (Activities of Daily Living), CGI (Investigator's Clinical Global Impression), SCAG (Sandoz Clinical Assessment - Geriatric) or NAI (Nuremberg Activities Inventory). Four included trials reported adverse events associated with Cerebrolysin in detail, while the other two (Vereschagin 1991; Liang 2001) did not provide any relevant information. None of the trials described data about all cause death, quality of life or carer burden measured with any valid questionnaire.

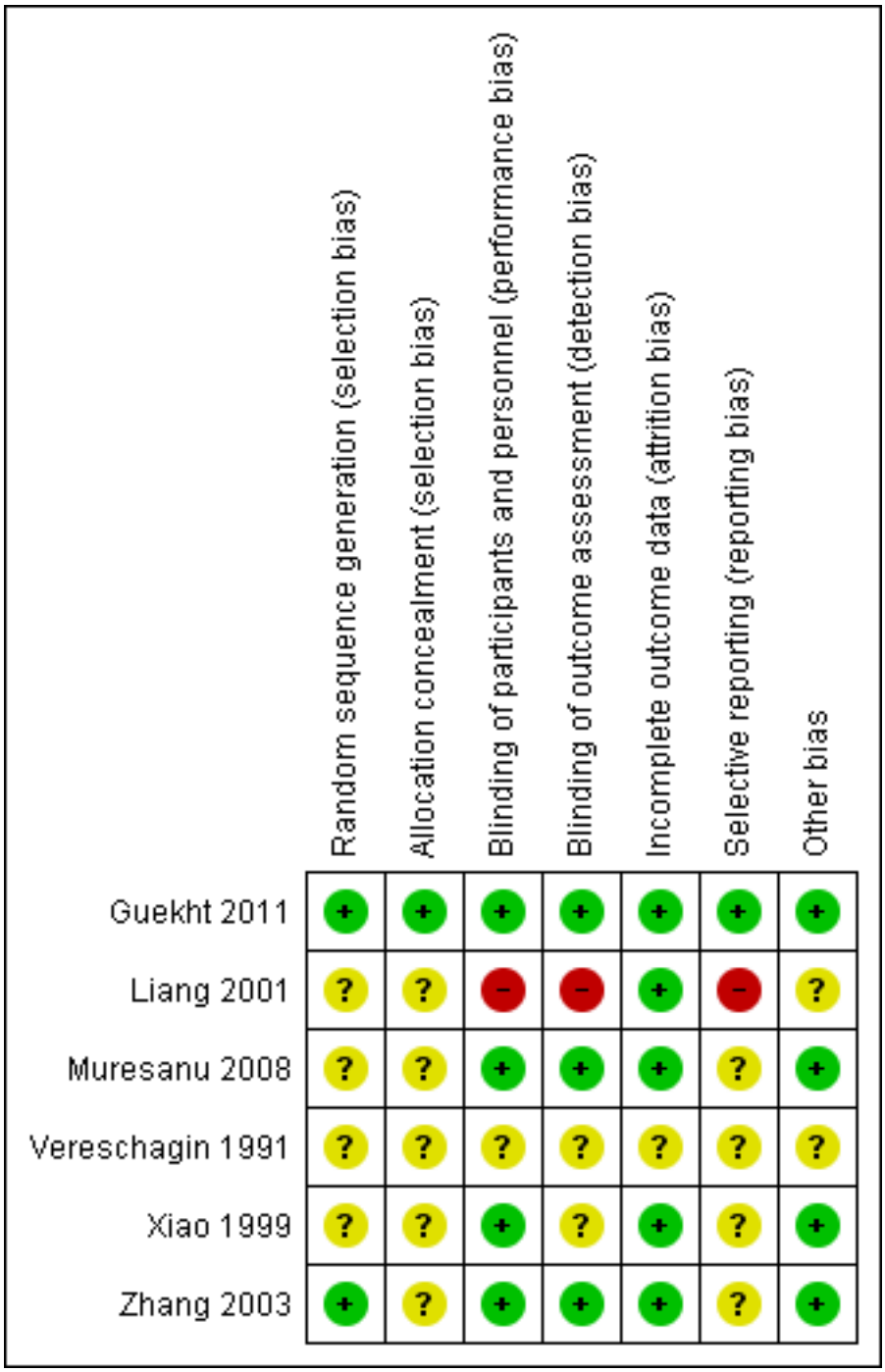
Excluded studies

Fifteen potentially relevant studies were excluded for one or more reasons as follows: not a RCT according to the full text (Meng 2001; Damulin 2008; Tapu 2009; Suvorova 2010); validated diagnostic criteria not used to identify patients with VaD (Zheng 1999; Cao 2000; Vereschagin 2001; Damulin 2008); another treatment, which might impact the effect, used in the control group but not the intervention group (Jia 1991; Li 1996; Wang 1996; Pan 1999; Wang 2003; Chen 2006; Dai 2011); Cerebrolysin used in both groups as a routine treatment (Xian 2004); outcomes evaluated with invalidated scales (Meng 2001).

Risk of bias in included studies

The risk of bias in included trials was evaluated in the following aspects: quality of randomization, allocation concealment, blinding of participants, personnel and outcome assessment, completeness of outcome data, selective reporting, etc. According to the summary assessment of the risk of bias for each important outcome (Higgins 2011b), one of the trials was rated as good quality (a low risk of bias) (Guekht 2011), four were rated as fair quality (an unclear risk of bias) (Vereschagin 1991; Xiao 1999; Zhang 2003; Muresanu 2008), and one as poor quality (a high risk of bias) (Liang 2001) (see Characteristics of included studies; Figure 1).

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



Allocation

All included trials stated they allocated participants to each study group randomly, but only two of them (Zhang 2003; Guekht 2011) provided information about the random sequence generation: Guekht and colleagues used a computer software (PROC PLAN in SAS version 8.2) to generate randomization code (Guekht 2011), and the Zhang study allocated patients by drawing lots (Zhang 2003). The Guekht study also specified that the random allocation sequence was concealed throughout the trial, using sealed, sequentially numbered, identical cardboard boxes containing blinded study medication according to the allocation sequence (Guekht 2011). However, insufficient descriptions in the reports could help us judge whether adequate allocation concealment was performed in the other five included trials (Vereschagin 1991; Xiao 1999; Liang 2001; Zhang 2003; Muresanu 2008).

Blinding

A double-blind design was used in five included trials (Vereschagin 1991; Xiao 1999; Zhang 2003; Muresanu 2008; Guekht 2011), of which three (Zhang 2003; Muresanu 2008; Guekht 2011) clearly stated that all participants and personnel involved in therapy performance and outcome assessment were blinded to treatment assignment during the entire study period. The Xiao study (Xiao 1999), stated as double-blind, used yellow opaque infusion bottles containing Cerebrolysin or placebo to secure blinding, which would indicate that the participants and personnel involved in treatment performance might be blinded to patients assignment, but whether the efficacy evaluators were also blinded could not be judged according to the reports. The Vereschagin study (Vereschagin 1991) just briefly referred to blinding method in broad terms as 'double-blind', but no other relevant information was available to tell who was blinded. The remaining trial (Liang 2001) was an unblinded study according to the full text: Cerebrolysin was an additional medication to routine treatment for ischemic stroke in the intervention group, whereas the control group was treated with routine treatment only without any placebo or blank solution, which made it impossible to perform blinding. Furthermore, the author did not use any term to suggest a blinding design in the article.

Incomplete outcome data

All included studies reported the duration of follow-up, which varied between trials. Three studies (Vereschagin 1991; Xiao 1999; Liang 2001) followed up participants less than one month after starting the treatment (15 days in the Liang 2001 trial and 4 weeks in the Vereschagin 1991 and Xiao 1999 trials). There were no dropouts in the first two studies, while one patient withdrew in the other trial (Xiao 1999) because of refusal of treatment, whose data were not included in the analyses. We found two reports of results in different phases of the Muresanu 2008 trial: the pilot phase evaluated the effects of Cerebrolysin after a four-week treatment, when no participants had been withdrawn (Muresanu 2008a); the extension study investigated efficacy outcomes through 12 weeks after the end of treatment, but eight participants (three and four in the two Cerebrolysin groups, respectively, and one in the placebo group) were lost to the follow-up visit, with balanced numbers and reasons between groups. Data on the remaining 33 patients were analysed (Muresanu 2010). The Guekht 2011 trial, with the largest sample size (242 participants in total), lost 25 patients during the entire 24-week study, and the number and reasons for discontinuation were similar in the two groups. Those withdrawn patients were still followed whenever possible to perform ITT analyses based on the last observation carried forward data, but patients included in the ITT analysis set should have received at least one dose of study medication and had a baseline plus at least one post-baseline assessment for both primary efficacy measures. As a result, four and six enrolled patients in each group were excluded from analysis. Although two patients were withdrawn because of adverse events, the risk of attrition bias due to incomplete outcome data was judged to be low since both of them were allocated to the placebo group. The sixth trial (Zhang 2003) with only 29 patients in a single center did not lose any of them although the study period was as long as three years. Missing data in the included trial reports were still unavailable for us to perform an ITT analysis in the present review.

Selective reporting

The study protocol is available for only one included trial (Guekht 2011) on the website of ClinicalTrials.gov. All of the study's pre-specified (both primary and secondary) outcome measures that are of interest in the present review were reported in the pre-specified way, which permitted us to judge its risk of bias due to selective reporting as low. We also made a judgement of 'High risk' in this aspect for one trial (Liang 2001), since it did not even mention the results for safety evaluation, which would be expected to have been reported as a key outcome for such an intervention study (Higgins 2011b). For the other four trials (Vereschagin 1991; Xiao 1999; Zhang 2003; Muresanu 2008), however, we could not make any clear judgement as 'Low' or 'High' risk of bias due to selective reporting, because their protocols were unavailable and insufficient information could be obtained.

Other potential sources of bias

Another potential risk of performance bias might come from a relaxed design of intervention in the Liang 2001 study. Patients

in both groups were treated with other medicine according to their condition, but which drugs were used were not recorded. Whether those drugs were balanced between groups or whether they would impact the results were not specified in the article. No other potential bias was found in four trials (Xiao 1999; Zhang 2003; Muresanu 2008; Guekht 2011) and insufficient information could be obtained from the other trial (Vereschagin 1991), which was only published in abstract form.

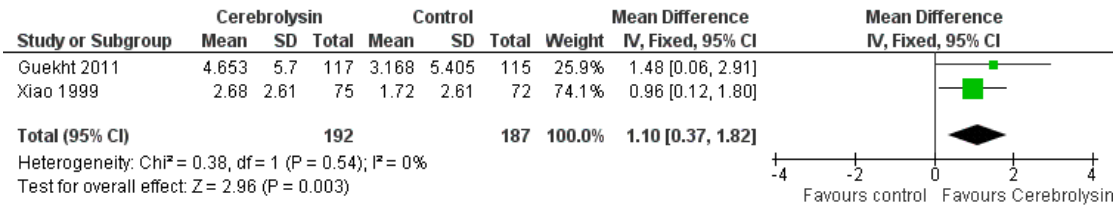
Effects of interventions

Primary outcomes

1. Cognitive function

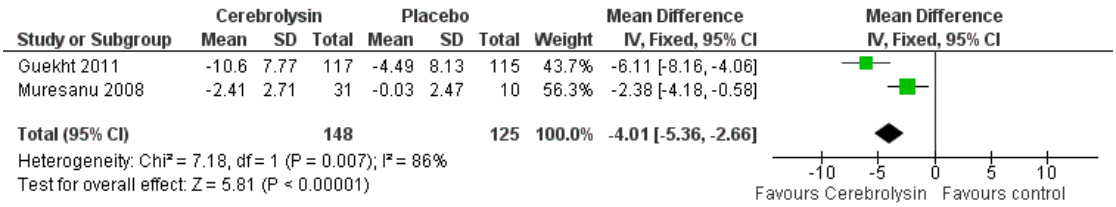
General cognitive function was evaluated as a primary efficacy parameter in all the included trials, but the instruments used and the type of data varied between trials. Two trials (Xiao 1999; Guekht 2011) with 379 participants evaluated the effect of Cerebrolysin on general cognitive function measured by the MMSE score-change from baseline. The Guekht 2011 trial used a dose of 20 ml daily over two treatment cycles (five days a week repeated for four weeks is one cycle), while the Xiao 1999 study used a daily dose of 30 ml for only one cycle. The Xiao 1999 trial reported means but not standard deviations for changes from baseline. However, it also reported the P value (0.028) for the comparison between groups, and so we could calculate the missing change-from-baseline standard deviation using the method described in Section 7.7.3.3 of the Cochrane *Handbook for Systematic Reviews of Interventions* (Higgins 2011c). The meta-analysis suggested a beneficial effect of Cerebrolysin on general cognitive function measured with the MMSE (WMD 1.10; 95% CI 0.37 to 1.82, P = 0.003; Analysis 1.1; Figure 2). Although the Zhang 2003 study also used the MMSE, it only reported response rates and not raw or change scores, so its data could not be included in this meta-analysis.

Figure 2. Forest plot of comparison: 1 Cognitive function, outcome: 1.1 The change of general cognitive function measured by MMSE.



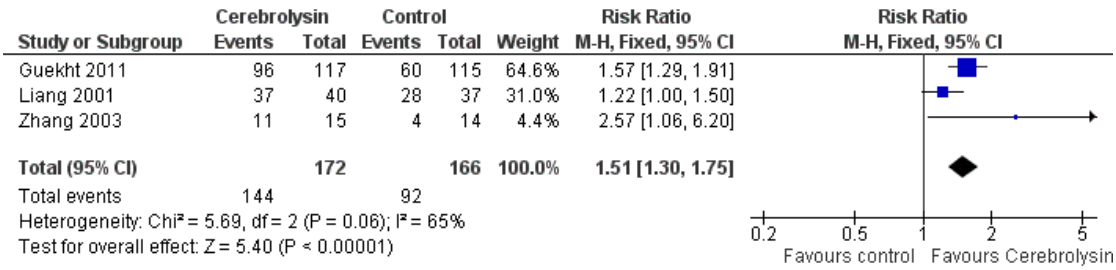
The effect on global cognitive function was also evaluated by the change of ADAS-cog+ scores in two trials (Muresanu 2008; Guekht 2011) with 273 patients. ADAS-cog+ is more sensitive in mild cognitive impairment than the original ADAS-cog version, since it covers three more cognitive domains (visual attention, executive function and delayed recall), impairments of which are commonly seen in patients with vascular cognitive dysfunction (Mohs 1997). For the Muresanu 2008 study we only included data from the four-week pilot study although relevant outcomes were measured through a 12-week extension, because the extension was open-label and nearly 20% of patients (8/41 in total, 3/16, 4/15 and 1/10 from the 10 ml Cerebrolysin, 30 ml Cerebrolysin, and placebo groups, respectively) were lost to follow-up, leading to high risks of detection and attrition bias. We combined the two experimental intervention groups treated by different doses of Cerebrolysin into a single group using the method described in the Cochrane *Handbook for Systematic Reviews of Interventions* (Higgins 2011d). This analysis also demonstrated a significant superiority of Cerebrolysin to placebo (WMD -4.01; 95% CI -5.36 to -2.66, P < 0.00001; Analysis 1.2; Figure 3). In the Zhang 2003 trial, authors reported the WISA scores at the end of three-year follow-up as well. Its results showed significant superiority of Cerebrolysin to control in most of the verbal and performance subtests, including information, comprehension, arithmetic, similarities, digit span, vocabulary, digit symbol, picture completion and picture arrangement (P < 0.05), but the full intelligence quotient (IQ) was not given or compared between groups in the report (Zhang 2003).

Figure 3. Forest plot of comparison: 1 Cognitive function, outcome: 1.2 The change of general cognitive function measured by ADAS-cog+ score.



Dichotomized data, for example the number of responders, allowed us to compare and pool data from trials using different measurement instruments. In the present review, for the ADAS-cog+, responders were defined as those with at least a 4-point improvement from baseline to the end of follow-up (Guekht 2011), and for the HDS and MMSE, responders were those with at least a 2-point increase compared to baseline (Liang 2001; Zhang 2003). All these definitions indicated a moderate to marked improvement in cognition from baseline. Data on response rates from three included trials (Liang 2001; Zhang 2003; Guekht 2011) with a total of 338 participants were pooled into a meta-analysis, which showed a statistically significant effect of Cerebrolysin on increasing the proportion of responders (RR 1.51; 95% CI 1.30 to 1.75, P < 0.00001; Analysis 1.3; Figure 4).

Figure 4. Forest plot of comparison: 1 Cognitive function, outcome: 1.3 The improvement of general cognitive function reported as responder rates.



Executive function, one of the specific cognitive functions commonly impaired in VaD, was evaluated in two included trials, using the Clock-Drawing Test and Trail-Making Test in the Guekht 2011 trial, and two Trail-Making Tests (ZVT-1 and ZVT-2) in the Xiao 1999 trial. We pooled the data on changes in Trail-Making Test time from the above two trials and found a significant reduction in time taken to complete the test after treatment with Cerebrolysin compared to the control group (WMD -22.36; 95% CI -34.48 to -10.23, P = 0.0003; Analysis 1.4). Comparing the Clock-Drawing Test scores between the two intervention groups in one trial (Guekht 2011) showed a treatment difference of 0.917 points (95% CI 0.448 to 1.387, P = 0.0002) in favour of Cerebrolysin, indicating a significant effect of Cerebrolysin in improving this executive function as well.

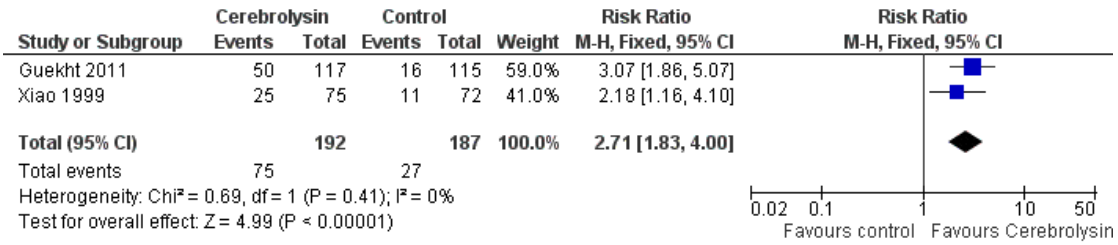
The remaining trial (Vereschagin 1991) was only reported as an abstract. Its authors stated that Cerebrolysin treatment resulted in significant improvement in memory, abstract thinking and re-

action time, confirmed by EEG-mapping, but detailed data were unavailable for any meta-analysis.

2. Global function

Improvement in global function was reported as response rates in two trials: in one trial investigators used the CIBIC+ scale (Guekht 2011), and CGI was used in the other one (Xiao 1999). To pool relevant data together, we defined responders as those with a CIBIC+ score of < 4 or those judged as at least moderately improved using the CGI rating at the last visit (Xiao 1999; Guekht 2011). The meta-analysis with 379 participants showed that Cerebrolysin was significantly beneficial for the improvement of global clinical function after one or more cycles of treatment (RR 2.71; 95% CI 1.83 to 4.00, P < 0.00001; Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: 2 Global function, outcome: 2.1 The improvement of global function reported as responder rates.



Changes in global functional performance were measured by ADL, NAI or SCAG scores in two included trials (Xiao 1999; Guekht 2011). In the former trial, Cerebrolysin was significantly superior to placebo (P < 0.0001) (Guekht 2011; Analysis 2.2), while no statistically significant difference was found between groups in the other study (ADL, P = 0.377; NAI, P = 0.355; SCAG, P = 0.767) (Xiao 1999). Since two quite different scales for evaluating such activities were used, we thought it was inappropriate to pool the data.

3. All cause death

Only one trial (Guekht 2011) specified that no deaths were reported during the experimental and follow-up periods. No data on all-cause mortality were available from the other included trials: three of them (Xiao 1999; Zhang 2003; Muresanu 2008) said no severe adverse effects were observed in either group, but did not mention deaths from other causes; the other two (Vereschagin 1991; Liang 2001) made no relevant comment in their articles.

Secondary outcomes

1. Adverse events

In the present review, adverse events were categorized as 'serious' or 'not serious'. Serious adverse events were those which led to death; were life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability; or any important medical event that might have jeopardized the patient or required intervention to prevent it. All other adverse events were considered to be non-serious (ICHEWG 1997).

Safety was assessed in four of the included trials (Xiao 1999; Zhang 2003; Muresanu 2008; Guekht 2011) by reporting adverse events, performing physical examinations or laboratory tests, or both. The relationship of adverse events and Cerebrolysin therapy was judged by investigators. The remaining two trials (Vereschagin 1991; Liang 2001) did not mention adverse events at all.

During the study period of the Guekht 2011 trial, some serious adverse events occurred, such as acute pyelonephritis, malignant

lung neoplasm, and rectosigmoid cancer (3/117 and 0/115 in the Cerebrolysin and placebo groups, respectively), but they were considered unrelated to the experimental treatment, and there was no significant difference between groups (RR 6.88; 95% CI 0.36 to 131.75, P = 0.20; Analysis 3.1). Three included trials (Xiao 1999; Zhang 2003; Muresanu 2008) observed no severe adverse effects in either group.

The most commonly reported non-serious adverse events were headache, asthenia, dizziness, hypertension and hypotension. Detailed data about the number of adverse events and patients reported in two trials (Xiao 1999; Guekht 2011) allowed us to perform a meta-analysis. The results indicated that these side effects were not statistically different between Cerebrolysin and control groups (RR 0.97; 95% CI 0.49 to 1.94, P = 0.94; Analysis 3.2; Figure 6). The Guekht 2011 trial also reported withdrawals due to adverse events, which were balanced between groups (1.7 % for the Cerebrolysin group and 2.5% for the control group) with a P value of 0.67 (Analysis 3.3). The Muresanu 2008 trial only stated that no severe adverse events occurred, and no significant differences in non-serious adverse events were found between groups, but relevant data were unavailable. Zhang and colleagues specified that no related adverse events were found during the three-year experimental period (Zhang 2003).

Figure 6. Forest plot of comparison: 4 Adverse events, outcome: 4.1 Non-serious adverse events.

The Xiao 1999 and Guekht 2011 trials also reported the change in laboratory parameters, including hematology, clinical chemistry, urinalysis, and electrocardiogram, and revealed no relevant differences between groups.

2. Quality of life

No data on quality of life during the treatment and follow-up periods were available from any of the included trials.

3. Carer burden

No data on evaluation of caregiver burden were available from the included trials.

Subgroup analyses

Significant heterogeneity was present in the analysis for the change of general cognitive function measured by ADAS-cog+ score (Analysis 1.2, I^2 = 86%) and for non-serious adverse events (Analysis 3.2, I^2 = 59%). Both might attribute to various treatment durations and follow-up periods (4 to 24 weeks) of included trials, so we undertook subgroup analyses for all outcome measures based on duration of treatment if possible.

Short-term treatment duration (only one treatment cycle or four weeks or less)

In four included trials, Cerebrolysin or placebo was given to participants for only one treatment cycle (five days a week repeated for four weeks) (Xiao 1999; Muresanu 2008) or four continuous weeks or less (Vereschagin 1991; Liang 2001). There was a slight beneficial effect of short-term treatment with Cerebrolysin on general cognitive function measured by MMSE score in one study (WMD 0.96; 95% CI 0.12 to 1.80, P = 0.03; Analysis 4.1) and ADAS-cog+ score in another study (WMD -2.38; 95% CI -4.18 to -0.58, P = 0.01; Analysis 4.2). However, a continuous 15-day treatment with Cerebrolysin had no significant effect on the response rate as measured by the HDS (RR 1.22; 95% CI 1.00 to 1.50, P = 0.05; Analysis 4.3). In one study, Cerebrolysin was significantly beneficial for global clinical impression after one cycle of treatment (RR 2.18; 95% CI 1.16 to 4.10, P = 0.02; Analysis 4.4), again in a single study. The same study reported non-serious side effects and found no significant difference between groups (RR 0.48; 95% CI 0.15 to 1.52, P = 0.21; Analysis 4.5).

Longer treatment duration (two or more treatment cycles or more than four weeks)

Two trials of longer duration administered Cerebrolysin over a total of 24 weeks (Guekht 2011) and three years (Zhang 2003), respectively. In these studies, Cerebrolysin was significantly better than placebo for global cognitive function measured by MMSE (WMD 1.48; 95% CI 0.06 to 2.91, P = 0.04; Analysis 4.1) (one study), ADAS-cog+ scores (WMD -6.11; 95% CI -8.16 to -4.06, P < 0.00001; Analysis 4.2) (one study), or by responder rates (RR 1.64; 95% CI 1.35 to 1.98, P < 0.00001; Analysis 4.3) (two studies). Two cycles of treatment with Cerebrolysin over 24 weeks also significantly improved clinically assessed global function of patients with VaD (WMD 3.07; 95% CI 1.86 to 5.07, P < 0.0001; Analysis 4.4), and led to no significant difference in occurrence of non-serious side effects between the Cerebrolysin and control groups (RR 1.54; 95% CI 0.62 to 3.84, P = 0.35; Analysis 4.5).

Sensitivity analyses

Based on the methodological quality, we also undertook sensitivity analyses for each outcome measure, for which meta-analysis pooled data from more than one trial. Since only one included study (Guekht 2011) of the present review was rated as good quality, we repeated the calculation after omitting all the other trials of fair or poor quality. However, the overall results and conclusions remained unchanged (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6).

DISCUSSION

Cerebrolysin seemed to be a promising intervention for treating vascular cognitive impairment based on reports of neurotrophic and pro-cognitive effects, but relevant studies yielded inconsistent results of such efficacy, thus prompting the present systematic review of randomized controlled trials. We have done our best to collect and extract all possible data to conduct a more complete systematic analysis.

Summary of main results

We performed a systematic search and selection process following the protocol, and then included six randomized controlled trials (Vereschagin 1991; Xiao 1999; Liang 2001; Zhang 2003; Muresanu 2008; Guekht 2011) which evaluated the efficacy of Cerebrolysin for VaD. Despite different designs, methods and durations of follow-up, sufficient similarities (such as definitive diagnosis and similar degree of VaD, consistent outcome measures and widely acceptable evaluative instruments, and the treatment regimen, etc) in the included studies allowed several meta-analyses to be conducted.

The primary outcome we always focus on for the treatment of patients with dementia is the improvement of cognitive function. The results of our review revealed that, for patients with VaD, Cerebrolysin could significantly improve both general cognitive function and a specific cognitive function commonly impaired in VaD, namely executive function, measured by mean scores on evaluation scales or by responder rates. It also improved patients' global function measured by CIBIC+ or CGI scales. The subgroup analyses based on varied treatment durations suggested a larger effect of long-term treatment than short-term therapy, which resulted in no or slight beneficial effect on both general cognitive function and global clinical impression. For the daily functional performance evaluated by ADL scales, however, results from two included trials (Xiao 1999; Guekht 2011) differed, but the different measurement scales used in the two trials did not allow us to perform a meta-analysis. Both trials had a relatively large sample (232 and 147 participants, respectively) and were of good or fair methodological quality, so we draw no conclusion about the effect on functional performance. No data on quality of life or caregiver burden were available from any of the included trials. In summary, we found positive results for Cerebrolysin compared to placebo or no treatment on most of the efficacy measures.

No serious adverse effects attributable to the experimental therapy were reported in these trials during the treatment and follow-up periods, and non-serious adverse effects were not significantly more common amongst the Cerebrolysin than the control participants. This indicated that Cerebrolysin was safe and well tolerated by patients with VaD.

Overall completeness and applicability of evidence

Most of the included trials addressed relevant functional endpoints for VaD and reported on adverse effects, but there were no data on quality of life or caregiver burden. Of the six included trials, two only enrolled patients diagnosed with multi-infarct dementia (Vereschagin 1991; Liang 2001), but lack of data meant that these two trials were not included in most of the meta-analyses, except the analysis of the improvement of general cognitive function reported as responder rates (data from Liang 2001 were included; Analysis 1.3). The other four trials (Xiao 1999; Zhang 2003; Muresanu 2008; Guekht 2011) included participants with any subtype of VaD of mild to moderate severity. The mean age of participants ranged from 60 to 70 years. So the results of the present review were mainly based on older patients with mild to moderate VaD, for whom we could draw conclusions. Relevant results could not be determined for patients with any particular kind of VaD.

As mentioned above, Cerebrolysin is recommended to be given once daily in a dose of 10 ml to 30 ml intravenously; one regular treatment cycle means five days a week repeated for four weeks, and two to four treatment cycles might be repeated per year (www.ebewe-neuro.com). Appropriate doses and administration method were used for all the included trials, but the duration of each treatment cycle and its repetition varied between trials.

Two trials treated patients for a single cycle (Xiao 1999; Muresanu 2008) and one for two cycles separated by an eight-week interval (Guekht 2011). The longest trial (Zhang 2003) used a continuous 10 days as one treatment cycle, and repeated it twice each year for a total of three years, but it had a small sample of 29 participants. The other two trials treated participants for 15 (Liang 2001) and 28 days (Vereschagin 1991) continuously. This review does not allow us to give a recommendation for the optimum treatment schedule. The variety of follow-up durations in the included trials made it difficult to evaluate outcomes at a single time point. We selected the longest follow-up (from 15 days to 3 years) from each study and pooled their outcome data in meta-analyses. This might induce a lack of consistency across studies, giving rise to heterogeneity, so we performed subgroup analyses based on treatment duration. Most conclusions for the outcome measures did not change; only the analysis (Analysis 4.3) for the improvement of general cognitive function reported as responder rates after a short-term treatment with Cerebrolysin did not get a positive result, but this result came from the only trial of short-term follow-up and poor methodological quality (Liang 2001). In practice, therapy for patients with VaD is long-term, so large-sample and long-term follow-up studies of good quality are still needed; optimum treatment schedule should be tested as well.

Further, to improve patients' quality of life and to reduce carers' burden are two of the most important goals for VaD treatment, but there was a lack of relevant data from included trials. Therefore, we could not draw any conclusions about these outcomes.

Quality of the evidence

All six included studies were randomized controlled trials. However, only one trial (Guekht 2011) was rated as good quality because of its design and endeavour to avoid selection, performance, detection, attrition, reporting and other bias. One was rated as poor quality (Liang 2001), since there was high risk of bias due to its poor performance in blinding and selective reporting. The other four trials were rated as fair because they had an unclear risk of bias for one or more key domains, commonly for allocation concealment, blinding of participants and personnel, or incomplete outcome data. Although the overall results and conclusions did not change in the sensitivity analyses based on methodological quality, all the results of meta-analyses in the present review were based on data from a single trial or several trials with a limited number of participants. Hence, the identified evidence did not permit a totally robust conclusion to be reached on the efficacy of Cerebrolysin for treating VaD.

Potential biases in the review process

We have attempted to do our best to search the pertinent literature, including published and unpublished studies, without any language restrictions, and contacted the investigators, as required to acquire additional information. Publication bias should still be taken into account, however, because most of the included studies were published in English or Chinese, and not enough useful information was sent back from the trial authors. It was impossible to perform a funnel plot analysis to evaluate the risk of publication bias because of the limited number of trials for each outcome measure.

Agreements and disagreements with other studies or reviews

A large, non-comparative study (Rainer 1997) with 645 participants also evaluated the efficacy of Cerebrolysin in patients with dementia, including 53% patients with VaD. A 10 ml to 15 ml daily dose of Cerebrolysin was given for at least seven days (mean treatment duration of 17.8 days). Its results showed that improvement in symptoms were found in 47% to 65% of participants, and approximately 80% patients were deemed to improve in global clinical function measured by CGI. Several non-systematic reviews (Plosker 2009; Plosker 2010) descriptively analyzed data from studies investigating Cerebrolysin in treating VaD, and most of them concluded that Cerebrolysin appeared to be a well tolerated and effective treatment option for VaD.

The findings are also supported by recording of the electroencephalogram (EEG) (Vereschagin 1991; Muresanu 2008a; Muresanu 2010). This was not evaluated in the present review, since it is not a direct measure of cognitive function. In patients with dementia, a patchy pattern of focal slowing is often recorded by EEG; it is thought to reflect changes in regional cerebral glucose metabolism (Renna 2003), and its main parameters, including delta power, theta power and power ratio (PR) scores, have been shown to correlate significantly with cognitive scores. The results of the Muresanu 2008 trial demonstrated a significant reduction of EEG PR scores after the therapy with Cerebrolysin, but no changes in the placebo-treated patients, in line with the reported improvement in cognitive function.

Data from other studies and reviews have shown positive clinical effects and good tolerability of Cerebrolysin in the treatment of AD (Álvarez 2006; Wei 2007; Álvarez 2011a; Álvarez 2011b). This is encouraging for VaD treatment since it has been gradually recognized that both neurodegenerative mechanisms and vascular factors contribute to the majority of cases of dementia, with a different relative weight in AD and VaD; in fact, mixed dementia may be the most common type of dementia (Moorhouse 2008; Viswanathan 2009).

AUTHORS' CONCLUSIONS

Implications for practice

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.

Implications for research

Well-designed, randomized, placebo-controlled trials of Cerebrolysin for dementia, with a greater number of participants and relatively long-term follow-up, are needed to evaluate the efficacy and detect the adverse events of Cerebrolysin in treating patients with VaD. Future investigators should pay more attention to the exploration of appropriate treatment schedules, evaluation of quality of life and caregiver burden. VaD can also occur in younger people, so young patients fulfilling the diagnosis criteria should not be excluded, but be stratified for assessment. Moreover, the quality of reporting should be improved, so that more useful data can be obtained.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Guekht 2011

Methods	Randomized: PROC PLAN in SAS version 8.2 (SAS Institute, Cary NC) was used for randomization, and the random allocation sequence was concealed throughout the trial through the use of sealed, sequentially numbered, identical cardboard boxes containing blinded study medication according to the allocation sequence Double-blind Placebo-controlled Duration: 24 weeks ITT analyses were performed, and the LOCF method was applied to account for missing data
Participants	Country: multiple centers in the Russian Federation. Number of participants: 242 patients entered the study, and 232 (145 post-menopausal female, 87 male) were included in the ITT analyses Age: average: 67.3 ± 8.0 years. Inclusion: mild to moderately severe VaD according to NINDS-AIREN criteria, with a MMSE score of 10 to 24, a modified Hachinski Ischemic Score of > 4 and a Hamilton Depression Rating Scale score of ≤15 Exclusion: patients with severe concomitant neurologic or psychiatric illnesses, any significant systemic illness or unstable medical condition that could lead to difficulty complying with the protocol, or a history of systemic cancer within the preceding 2 years Baseline: the study groups had similar demographic and other baseline characteristics
Interventions	Cere group: Cere 20 ml + physiological saline 80 ml Placebo group: physiological saline 100 ml i.v. infusions once daily, 5 days/week for 4 weeks, followed by a 2-month treatment-free interval (weeks 5 to 12) and then resumption of the 5-day-per-week schedule (weeks 13 to 16), for a total of 40 infusions
Outcomes	ADAS-cog+ score CIBIC+ score CIBIS+ score MMSE ADCS-ADL Trail-Making Test A Clock-Drawing Test Safety assessment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Guekht 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	PROC PLAN in SAS version 8.2 (SAS Institute, Cary NC) was used for randomization
Allocation concealment (selection bias)	Low risk	The random allocation sequence was concealed throughout the trial through the use of sealed, sequentially numbered, identical cardboard boxes containing blinded study medication according to the allocation sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All patients and therapy providers were blinded to treatment assignment during the entire study period
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study personnel who assessed outcomes were also blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of missing data and reasons were reported and similar in each group, and ITT analyses were performed
Selective reporting (reporting bias)	Low risk	The study protocol is available and all the pre-specified outcomes that are of interest in the present review were all reported
Other bias	Low risk	No other potential bias was found.

Liang 2001

Methods	Randomized: methods of randomization and allocation concealment were not described Non-blind Blank-controlled Duration: 15 days. ITT analysis: none was lost to follow-up.
Participants	Country: single center in China. Number of participants: 77 patients (23 female and 54 male). Age: average: 60.4 years in the Cere group, 61.2 years in the control group Inclusion: mild to moderately severe VaD according to DSM-IIIR and ICD-10 criteria, with a Hachinski score of ≥ 7 Exclusion: not specified. Baseline:the study groups had similar baseline characteristics
Interventions	Cere group: Cere 20 ml + physiological saline 200 ml + routine treatment Control group: routine treatment

Liang 2001 (*Continued*)

	Cere were administered by i.v. infusions once daily for 15 days	
Outcomes	HDS	
Notes	Patients in both groups were treated with other medicine according to patients' condition, but whether those drugs were balance between groups or whether they would impact the results were not specified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was not any blind design according to the article, and placebos or blank controlled solutions were not used for blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was not any blind design according to the article, and placebos or blank controlled solutions were not used for blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the enrolled patients was lost to the study.
Selective reporting (reporting bias)	High risk	The study protocol is not available. The only outcome measure listed in the *Outcome* section was reported, but it did not mention the safety results, which would be expected to have been reported for such a study
Other bias	Unclear risk	Patients in both groups were treated with other medicine according to patients' condition, but whether those drugs were balanced between groups or whether they would impact the results were not specified

Muresanu 2008

Methods	Randomized: 2:3:3 randomization ratio (i.e. 31 patients were randomized to three groups: 10 patients in placebo group, 16 in Cere10 group, and 15 in Cere30 group); the method of randomization and concealment was not described Double-blind Placebo-controlled Duration: a total of 16 weeks (a 4-week treatment period, followed by a 12-week, open-label extension); only data from the 4-week treatment period were included in meta-analyses of the present review ITT analysis: not performed, although 8 patients (3, 4 and 1 from the Cere10, Cere30 and placebo groups, respectively) were lost to the follow-up visit
Participants	Country: Romania. Number of participants: 41 (21 post-menopausal female, 20 male) Age: average: 70.7 ± 1.6 years; range: 51 to 88 years. Inclusion: mild to moderately severe probable VaD according to NINDS-AIREN criteria, MMSE between 9 and 26 Exclusion: non-VaD dementia, current or past significant neurological diseases other than VaD, major depression, psychosis, substance dependence, laboratory abnormalities clinically relevant for dementia or significant concomitant illnesses Baseline:demographic data and disease characteristics were not different significantly between groups
Interventions	Cere10 group: Cere 10 ml + physiological saline 40 ml Cere30 group: Cere 30 ml + physiological saline 20 ml Control group: normal physiological saline 50 ml i.v. infusions once daily and 5 days/week for 4 weeks.
Outcomes	ADAS-cog+ scores qEEG PR scores Adverse events
Notes	All the randomized patients completed the study and all were included in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described in the article
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described in the article
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patients and implementers were blinded of the treatment assigned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The evaluators were blinded of the treatment assigned.

Incomplete outcome data (attrition bias) All outcomes	Low risk	All the randomized patients completed the 4-week treatment and evaluation, and number of loss from the 12-week extension study and reasons were similar in each group
Selective reporting (reporting bias)	Unclear risk	Outcomes listed in the *treatment efficacy measures* section were all reported, but the study protocol is unavailable, so there was insufficient information to permit a clear judgement
Other bias	Low risk	No other potential bias was found.

Vereschagin 1991

Methods	Randomized: methods of randomization and allocation concealment were not described Double-blind Placebo-controlled Duration: 4 weeks
Participants	Number of participants: 60 patients were divided equally into two groups Inclusion: patients with a mild form of multi-infarct dementia, but the diagnosis criteria were not described Baseline:the study groups had similar baseline compared parameters
Interventions	Cere group: Cere 15 ml (10 ml in the morning and 5 ml in the evening) + 0.85% NaCl solution 200 ml Placebo group: placebo 15 ml (10 ml in the morning and 5 ml in the evening) + 0.85% NaCl solution 200 ml i.v. infusions twice daily for 28 days.
Outcomes	Clinical evaluations (by means of a special scale) EEG Psychological test of Arnold-Kohlmann Test for response time
Notes	Only an abstract was found. Detailed information could not be obtained in spite of our efforts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Detailed methods were not obtained.

Vereschagin 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Detailed methods were not obtained.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Detailed methods were not obtained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Detailed methods were not obtained.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details were not obtained.
Selective reporting (reporting bias)	Unclear risk	Details were not obtained.
Other bias	Unclear risk	Details were not obtained.

Xiao 1999

Methods	Randomized: the methods of randomization and allocation concealment were not described Double-blind: details were not described. Placebo-controlled Duration: 4 weeks ITT analysis: not performed; one patient who refused the treatment was excluded from the analyses
Participants	Country: multiple centers in China. Number of participants: 148 patients were enrolled, and 147 completed the study (45 female who were post-menopausal or had been surgically sterilized prior to entry, 102 male) Age: average: 69.88 ± 6.33 years in the Cere group, 69.60 ± 7.22 years in the placebo group; range: 55 to 85 years Inclusion: mild to moderately severe VaD according to DSM-IV criteria, with a MMSE score of 15-25, a Hachinski score of $\geq$ 7, a GDS rating of 3 to 5, and a Hamilton Depression Rating Scale score of $\leq$ 15 Exclusion: patients with evidence of other psychiatric or neurological disorders and had clinically significant or active renal, hepatic, endocrine, or cardiovascular diseases; patients with severe heart disease, severe hypertension and severe obstructive pulmonary disease, hematological or oncological disorders, or vitamin B12 or folate deficiency; patients receiving other nootropic agents, psychotropic drugs, hypnotics, drugs influencing cerebral blood flow, or stimulants Baseline: the study groups had similar baseline characteristics
Interventions	Cere group: Cere 30 ml + physiological saline 100 ml Placebo group: placebo 30 ml + physiological saline 100 ml i.v. infusions once daily, 5 days/week for 4 weeks.

Xiao 1999 (*Continued*)

Outcomes	MMSE Investigator's Clinical Global Impression Trail Making Test Sandoz Clinical Assessment - Geriatric Activities of Daily Living Self-reported Nuremberg Activities Inventory Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described in the article
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described in the article
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was stated as double-blind, and yellow opaque infusion bottles containing Cerebrolysin or placebo were used, which indicated that the participants and personnel involved in administering treatment might be blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was stated as double-blind, but the details were not described, so whether the outcome assessment was blinded remained unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one patient who refused the treatment was excluded, but which group he or she was allocated to was not reported
Selective reporting (reporting bias)	Unclear risk	The study protocol is unavailable, so there was insufficient information to permit a clear judgement
Other bias	Low risk	No other potential bias was found.

Zhang 2003

Methods	Randomized: enrolled patients were allocated randomly by drawing lots, but the method of allocation concealment was not described Double-blind: it was stated that patients and investigators were blinded during the interventions and evaluations Blank-controlled Duration: 3 years ITT analysis: none was lost to follow-up.
Participants	Country: single center in China. Number of participants: 29 patients (3 female and 26 male). Age: average: 70.80 ± 6.69 years in the Cere group, 69.51 ± 7.02 years in the control group Inclusion: mild to moderately severe VaD according to DSM-IV criteria, with a Hachinski score of ≥ 7. Dementia occurred within 3 months after the onset of confirmed cerebral vascular disease, and the manifestations persisted for more than 3 months Exclusion: patients with evidence of other kinds of dementia, with severe cardiac, cerebral or renal dysfunction, severe psychiatric disorders or diabetes mellitus, and patients who had recently received other treatments for dementia Baseline: the study groups had similar baseline characteristics
Interventions	Cere group: Cere 20 ml + Xuesaitong (a traditional Chinese patent medicine) 0.4 g + physiological saline 250 ml or 50 g/l glucose solution 250 ml Control group: Xuesaitong (a traditional Chinese patent medicine) 0.4 g + physiological saline 250 ml or 50 g/l glucose solution 250 ml i.v. infusions 60-120 min once daily, 10 days for each course and one course in each spring and autumn; in total 6 courses for the whole 3 years
Outcomes	MMSE WISA-RC
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were allocated randomly by drawing lots.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was stated that patients and investigators were blinded during the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was stated that patients and investigators were blinded during the evaluations

Zhang 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the 29 enrolled patients was lost to the study or follow-up
Selective reporting (reporting bias)	Unclear risk	The study protocol is unavailable, so there was insufficient information to permit a clear judgement
Other bias	Low risk	No other potential bias was found.

ITT: intention-to-treat; LOCF: last observation carried forward; VaD: vascular dementia; NINDS-AIREN: National Institute of Neurologic Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; MMSE: Mini-Mental State Examination; Cere: Cerebrolysin; i.v.: intravenous injection; ADAS-cog+: Alzheimer's Disease Assessment Scale Cognitive Subpart, Extended Version; CIBIC+: Clinician's Interview-Based Impression of Change plus Caregiver Input; CIBIS+: Clinician's Interview-Based Impression of Severity; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Disease; HDS: Hasegawa Dementia Scale; qEEG: quantitative electroencephalogram; PR: power ratio; GDS: Global Deterioration Scale; WISA-RC: Wechsler Intelligence Scale for Adult - Revised for Chinese; NaCl: sodium chloride.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cao 2000	This study enrolled patients with cerebrovascular disease, and information of patients with so-called vascular dementia could be extracted, but there was no validated inclusion criteria for patients' enrolment. Patients who were diagnosed with multiple infarcts or angiosclerosis in brain and with dementia could be enrolled, which we judged as an unacceptable criterion
Chen 2006	The control group used cytidine diphosphate choline, which was not used in the Cerebrolysin group
Dai 2011	The control group used cytidine diphosphate choline, which was not used in the Cerebrolysin group
Damulin 2008	According to the full text, it was a non-RCT, and the enrolled patients were not diagnosed with dementia
Jia 1991	The control group used cytidine diphosphate choline and piracetam, which was not used in the Cerebrolysin group
Li 1996	The control group used cytidine diphosphate choline, which was not used in the Cerebrolysin group
Meng 2001	It was judged as a non-RCT after we read the full text, and a non-validated scale was used to evaluate the outcomes
Pan 1999	The controlled group used piracetam, which was not used in the Cerebrolysin group
Suvorova 2010	It was a non-randomized trial according to the description.

(*Continued*)

Tapu 2009	Two lots of patients were enrolled into the placebo and treatment groups, respectively, which indicated that patients were not allocated to either group by random
Vereschagin 2001	The subjects were patients with cognitive disorders and arterial hypertension and atherosclerosis, but the diagnosis of dementia was not made
Wang 1996	Cytidine diphosphate choline and Cerebrolysin were used in the treatment group and control group, respectively, which did not fulfil our inclusion criteria
Wang 2003	The control group used cytidine diphosphate choline, which was not used in the Cerebrolysin group
Xian 2004	Cerebrolysin was used in both groups as a routine treatment.
Zheng 1999	Patients who were diagnosed with cerebrovascular disease and with dementia could be enrolled, which we judged as an unacceptable criterion

DATA AND ANALYSES

Comparison 1. Cognitive function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The change of general cognitive function measured by MMSE	2	379	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.37, 1.82]
2 The change of general cognitive function measured by ADAS-cog+ score	2	273	Mean Difference (IV, Fixed, 95% CI)	-4.01 [-5.36, -2.66]
3 The improvement of general cognitive function reported as responder rates	3	338	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.30, 1.75]
4 The change of executive function measured by the Trail-Making Test	2	526	Mean Difference (IV, Fixed, 95% CI)	-22.36 [-34.48, -10.23]

Comparison 2. Global function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The improvement of global function reported as responder rates	2	379	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [1.83, 4.00]
2 The change of global function measured by ADCS-ADL score	1	232	Mean Difference (IV, Fixed, 95% CI)	6.32 [4.20, 8.45]

Comparison 3. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	1	232	Risk Ratio (M-H, Fixed, 95% CI)	6.88 [0.36, 131.75]
2 Non-serious adverse events	2	379	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.49, 1.94]
3 Withdrawals due to adverse events	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.25, 8.66]

Comparison 4. Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The change of general cognitive function measured by MMSE	2	379	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.37, 1.82]
1.1 Short-term treatment	1	147	Mean Difference (IV, Fixed, 95% CI)	0.96 [0.12, 1.80]
1.2 Long-term treatment	1	232	Mean Difference (IV, Fixed, 95% CI)	1.48 [0.06, 2.91]
2 The change of general cognitive function measured by ADAS-cog+ score	2	273	Mean Difference (IV, Fixed, 95% CI)	-4.01 [-5.36, -2.66]
2.1 Short-term treatment	1	41	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-4.18, -0.58]
2.2 Long-term treatment	1	232	Mean Difference (IV, Fixed, 95% CI)	-6.11 [-8.16, -4.06]
3 The improvement of general cognitive function reported as responder rates	3	338	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.30, 1.75]
3.1 Short-term treatment	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.00, 1.50]
3.2 Long-term treatment	2	261	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.35, 1.98]
4 The improvement of global function reported as responder rates	2	379	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [1.83, 4.00]
4.1 Short-term treatment	1	147	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.16, 4.10]
4.2 Long-term treatment	1	232	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [1.86, 5.07]
5 Non-serious adverse events	2	379	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.49, 1.94]
5.1 Short-term treatment	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.15, 1.52]
5.2 Long-term treatment	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.62, 3.84]

Comparison 5. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The change of general cognitive function measured by MMSE	1	232	Mean Difference (IV, Fixed, 95% CI)	1.48 [0.06, 2.91]
2 The change of general cognitive function measured by ADAS-cog+ score	1	232	Mean Difference (IV, Fixed, 95% CI)	-6.11 [-8.16, -4.06]
3 The improvement of general cognitive function reported as responder rates	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.29, 1.91]
4 The change of executive function measured by the Trail-Making Test	1	232	Mean Difference (IV, Fixed, 95% CI)	-15.31 [-30.19, -0.43]
5 The improvement of global function reported as responder rates	1	232	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [1.86, 5.07]
6 Non-serious adverse events	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.62, 3.84]

Analysis 1.1. Comparison 1 Cognitive function, Outcome 1 The change of general cognitive function measured by MMSE.

Review: Cerebrolysin for vascular dementia

Comparison: 1 Cognitive function

Outcome: 1 The change of general cognitive function measured by MMSE

Study or subgroup	Cerebrolysin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Guekht 2011	117	4.653 (5.7)	115	3.17 (5.405)		25.9 %	1.48 [0.06, 2.91]
Xiao 1999	75	2.68 (2.61)	72	1.72 (2.61)		74.1 %	0.96 [0.12, 1.80]
Total (95% CI)	**192**		**187**			**100.0 %**	**1.10 [0.37, 1.82]**

Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² =0.0%

Test for overall effect: Z = 2.96 (P = 0.0031)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Cognitive function, Outcome 2 The change of general cognitive function measured by ADAS-cog+ score.

Review: Cerebrolysin for vascular dementia

Comparison: 1 Cognitive function

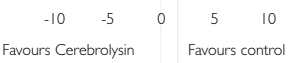
Outcome: 2 The change of general cognitive function measured by ADAS-cog+ score

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

Heterogeneity: Chi² = 7.18, df = 1 (P = 0.01); I² =86%

Test for overall effect: Z = 5.81 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Cognitive function, Outcome 3 The improvement of general cognitive function reported as responder rates.

Review: Cerebrolysin for vascular dementia

Comparison: 1 Cognitive function

Outcome: 3 The improvement of general cognitive function reported as responder rates

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio 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 (Cerebrolysin), 92 (Control)

Heterogeneity: $Chi^2 = 5.69$, df = 2 (P = 0.06); $I^2 = 65\%$

Test for overall effect: Z = 5.40 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Cognitive function, Outcome 4 The change of executive function measured by the Trail-Making Test.

Review: Cerebrolysin for vascular dementia

Comparison: 1 Cognitive function

Outcome: 4 The change of executive function measured by the Trail-Making Test

Study or subgroup	Cerebrolysin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Guekht 2011	117	-40.163 (57.828)	115	-24.85 (57.823)		66.4 %	-15.31 [-30.19, -0.43]
Xiao 1999 (1)	75	-50.23 (105.34)	72	-7.83 (105.34)		12.7 %	-42.40 [-76.46, -8.34]
Xiao 1999 (2)	75	-45.06 (81.88)	72	-12.51 (81.88)		21.0 %	-32.55 [-59.03, -6.07]
Total (95% CI)	**267**		**259**			**100.0 %**	**-22.36 [-34.48, -10.23]**

Heterogeneity: Chi^2 = 2.76, df = 2 (P = 0.25); I^2 =28%

Test for overall effect: Z = 3.61 (P = 0.00030)

Test for subgroup differences: Not applicable

(1) Measured by the ZVT-2.

(2) Measured by the ZVT-1.

Analysis 2.1. Comparison 2 Global function, Outcome 1 The improvement of global function reported as responder rates.

Review: Cerebrolysin for vascular dementia

Comparison: 2 Global function

Outcome: 1 The improvement of global function reported as responder rates

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio 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 (Cerebrolysin), 27 (Control)

Heterogeneity: $Chi^2 = 0.69$, df = 1 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 4.99 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Global function, Outcome 2 The change of global function measured by ADCS-ADL score.

Review: Cerebrolysin for vascular dementia

Comparison: 2 Global function

Outcome: 2 The change of global function measured by ADCS-ADL score

Study or subgroup	Cerebrolysin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Guekht 2011	117	7.264 (8.264)	115	0.94 (8.268)		100.0 %	6.32 [4.20, 8.45]
Total (95% CI)	**117**		**115**			**100.0 %**	**6.32 [4.20, 8.45]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.83 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Adverse events, Outcome 1 Serious adverse events.

Review: Cerebrolysin for vascular dementia

Comparison: 3 Adverse events

Outcome: 1 Serious adverse events

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Guekht 2011	3/117	0/115		100.0 %	6.88 [0.36, 131.75]
Total (95% CI)	**117**	**115**		**100.0 %**	**6.88 [0.36, 131.75]**

Total events: 3 (Cerebrolysin), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Adverse events, Outcome 2 Non-serious adverse events.

Review: Cerebrolysin for vascular dementia

Comparison: 3 Adverse events

Outcome: 2 Non-serious adverse events

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio 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 (Cerebrolysin), 15 (Control)

Heterogeneity: Chi^2 = 2.42, df = 1 (P = 0.12); I^2 =59%

Test for overall effect: Z = 0.08 (P = 0.94)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Adverse events, Outcome 3 Withdrawals due to adverse events.

Review: Cerebrolysin for vascular dementia

Comparison: 3 Adverse events

Outcome: 3 Withdrawals due to adverse events

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Guekht 2011	3/117	2/115		100.0 %	1.47 [0.25, 8.66]
Total (95% CI)	**117**	**115**		**100.0 %**	**1.47 [0.25, 8.66]**

Total events: 3 (Cerebrolysin), 2 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Subgroup analyses , Outcome 1 The change of general cognitive function measured by MMSE.

Review: Cerebrolysin for vascular dementia

Comparison: 4 Subgroup analyses

Outcome: 1 The change of general cognitive function measured by MMSE

Study or subgroup	Cerebrolysin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short-term treatment							
Xiao 1999	75	2.68 (2.61)	72	1.72 (2.61)		74.1 %	0.96 [0.12, 1.80]
Subtotal (95% CI)	**75**		**72**			**74.1 %**	**0.96 [0.12, 1.80]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.23 (P = 0.026)							
2 Long-term treatment							
Guekht 2011	117	4.653 (5.7)	115	3.17 (5.405)		25.9 %	1.48 [0.06, 2.91]
Subtotal (95% CI)	**117**		**115**			**25.9 %**	**1.48 [0.06, 2.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.04 (P = 0.042)							
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 =0.0%							
Test for overall effect: Z = 2.96 (P = 0.0031)							
Test for subgroup differences: Chi^2 = 0.38, df = 1 (P = 0.54), I^2 =0.0%							

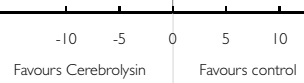
Analysis 4.2. Comparison 4 Subgroup analyses , Outcome 2 The change of general cognitive function measured by ADAS-cog+ score.

Review: Cerebrolysin for vascular dementia

Comparison: 4 Subgroup analyses

Outcome: 2 The change of general cognitive function measured by ADAS-cog+ score

Study or subgroup	Cerebrolysin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short-term treatment							
Muresanu 2008	31	-2.41 (2.71)	10	-0.03 (2.47)		56.3 %	-2.38 [-4.18, -0.58]
Subtotal (95% CI)	**31**		**10**			**56.3 %**	**-2.38 [-4.18, -0.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.59 (P = 0.0097)							
2 Long-term treatment							
Guekht 2011	117	-10.6 (7.77)	115	-4.49 (8.13)		43.7 %	-6.11 [-8.16, -4.06]
Subtotal (95% CI)	**117**		**115**			**43.7 %**	**-6.11 [-8.16, -4.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.85 (P < 0.00001)							
Total (95% CI)	**148**		**125**			**100.0 %**	**-4.01 [-5.36, -2.66]**
Heterogeneity: Chi^2 = 7.18, df = 1 (P = 0.01); I^2 =86%							
Test for overall effect: Z = 5.81 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 7.18, df = 1 (P = 0.01), I^2 =86%							



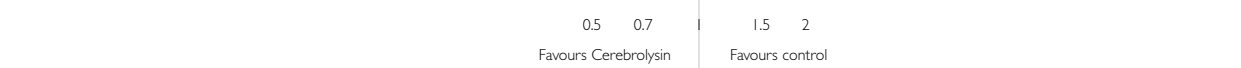
Analysis 4.3. Comparison 4 Subgroup analyses , Outcome 3 The improvement of general cognitive function reported as responder rates.

Review: Cerebrolysin for vascular dementia

Comparison: 4 Subgroup analyses

Outcome: 3 The improvement of general cognitive function reported as responder rates

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Short-term treatment					
Liang 2001	37/40	28/37		31.0 %	1.22 [1.00, 1.50]
Subtotal (95% CI)	**40**	**37**		**31.0 %**	**1.22 [1.00, 1.50]**
Total events: 37 (Cerebrolysin), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.052)					
2 Long-term treatment					
Guekht 2011	96/117	60/115		64.6 %	1.57 [1.29, 1.91]
Zhang 2003	11/15	4/14		4.4 %	2.57 [1.06, 6.20]
Subtotal (95% CI)	**132**	**129**		**69.0 %**	**1.64 [1.35, 1.98]**
Total events: 107 (Cerebrolysin), 64 (Control)					
Heterogeneity: Chi^2 = 1.16, df = 1 (P = 0.28); I^2 =14%					
Test for overall effect: Z = 5.03 (P < 0.00001)					
Total (95% CI)	**172**	**166**		**100.0 %**	**1.51 [1.30, 1.75]**
Total events: 144 (Cerebrolysin), 92 (Control)					
Heterogeneity: Chi^2 = 5.69, df = 2 (P = 0.06); I^2 =65%					
Test for overall effect: Z = 5.40 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 4.19, df = 1 (P = 0.04), I^2 =76%					



Analysis 4.4. Comparison 4 Subgroup analyses , Outcome 4 The improvement of global function reported as responder rates.

Review: Cerebrolysin for vascular dementia

Comparison: 4 Subgroup analyses

Outcome: 4 The improvement of global function reported as responder rates

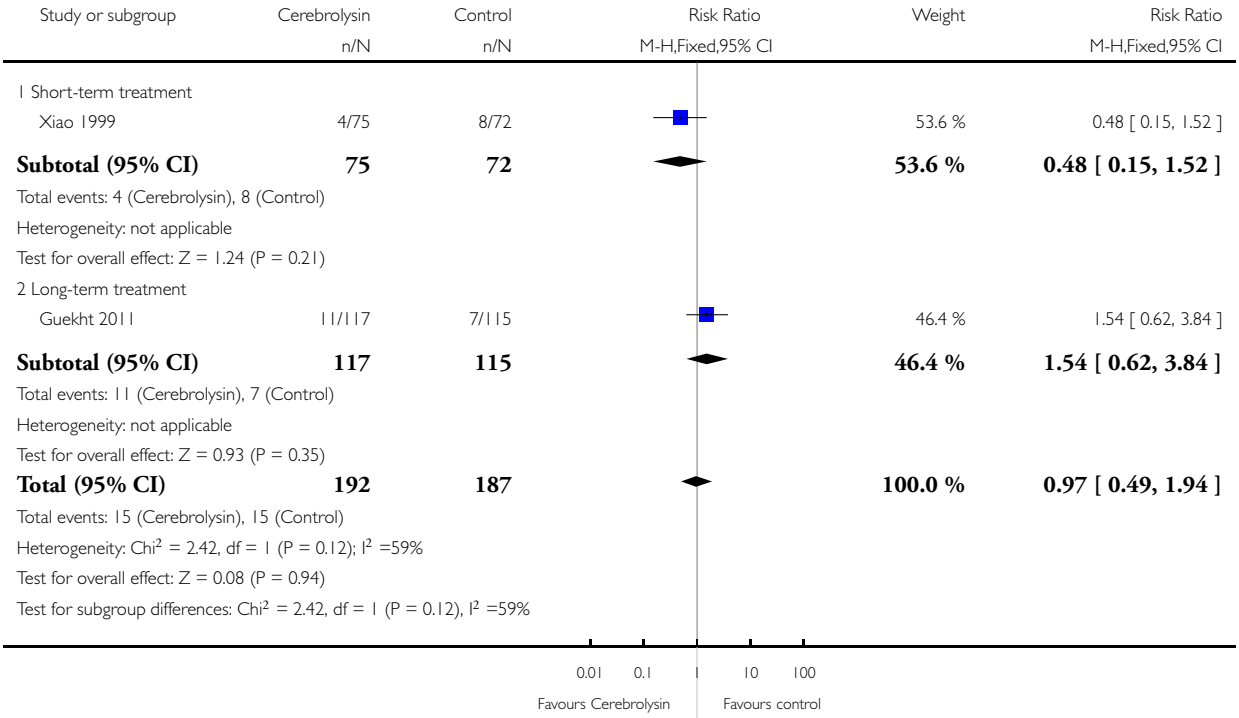
Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Short-term treatment					
Xiao 1999	25/75	11/72		41.0 %	2.18 [1.16, 4.10]
Subtotal (95% CI)	**75**	**72**		**41.0 %**	**2.18 [1.16, 4.10]**
Total events: 25 (Cerebrolysin), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.42 (P = 0.015)					
2 Long-term treatment					
Guekht 2011	50/117	16/115		59.0 %	3.07 [1.86, 5.07]
Subtotal (95% CI)	**117**	**115**		**59.0 %**	**3.07 [1.86, 5.07]**
Total events: 50 (Cerebrolysin), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.39 (P = 0.000011)					
Total (95% CI)	**192**	**187**		**100.0 %**	**2.71 [1.83, 4.00]**
Total events: 75 (Cerebrolysin), 27 (Control)					
Heterogeneity: Chi^2 = 0.69, df = 1 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 4.99 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.69, df = 1 (P = 0.41), I^2 =0.0%					

Analysis 4.5. Comparison 4 Subgroup analyses , Outcome 5 Non-serious adverse events.

Review: Cerebrolysin for vascular dementia

Comparison: 4 Subgroup analyses

Outcome: 5 Non-serious adverse events

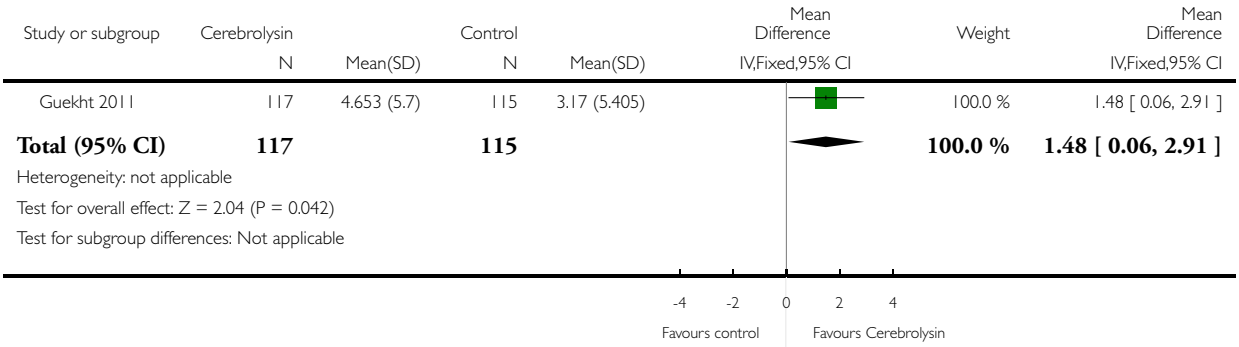


Analysis 5.1. Comparison 5 Sensitivity analyses, Outcome 1 The change of general cognitive function measured by MMSE.

Review: Cerebrolysin for vascular dementia

Comparison: 5 Sensitivity analyses

Outcome: 1 The change of general cognitive function measured by MMSE

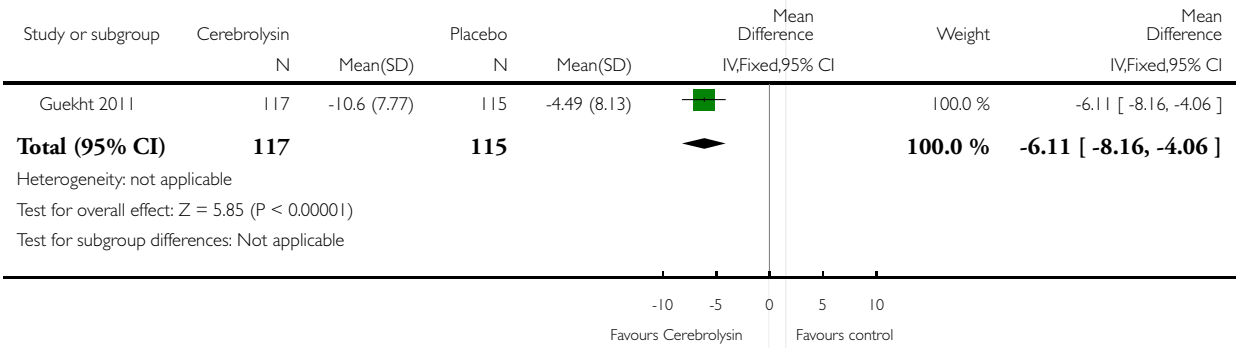


Analysis 5.2. Comparison 5 Sensitivity analyses, Outcome 2 The change of general cognitive function measured by ADAS-cog+ score.

Review: Cerebrolysin for vascular dementia

Comparison: 5 Sensitivity analyses

Outcome: 2 The change of general cognitive function measured by ADAS-cog+ score



Analysis 5.3. Comparison 5 Sensitivity analyses, Outcome 3 The improvement of general cognitive function reported as responder rates.

Review: Cerebrolysin for vascular dementia

Comparison: 5 Sensitivity analyses

Outcome: 3 The improvement of general cognitive function reported as responder rates

Study or subgroup	Cerebrolysin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Guekht 2011	96/117	60/115		100.0 %	1.57 [1.29, 1.91]
Total (95% CI)	**117**	**115**		**100.0 %**	**1.57 [1.29, 1.91]**
Total events: 96 (Cerebrolysin), 60 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.56 (P < 0.00001)					
Test for subgroup differences: Not applicable					

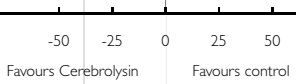
Analysis 5.4. Comparison 5 Sensitivity analyses, Outcome 4 The change of executive function measured by the Trail-Making Test.

Review: Cerebrolysin for vascular dementia

Comparison: 5 Sensitivity analyses

Outcome: 4 The change of executive function measured by the Trail-Making Test

Study or subgroup	Cerebrolysin N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Guekht 2011	117	-40.163 (57.828)	115	-24.85 (57.823)		100.0 %	-15.31 [-30.19, -0.43]
Total (95% CI)	**117**		**115**			**100.0 %**	**-15.31 [-30.19, -0.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.02 (P = 0.044)							
Test for subgroup differences: Not applicable							

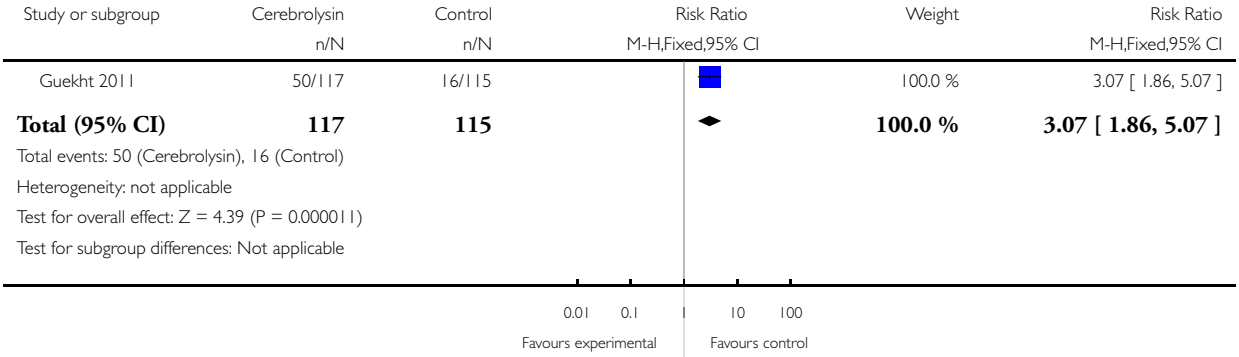


Analysis 5.5. Comparison 5 Sensitivity analyses, Outcome 5 The improvement of global function reported as responder rates.

Review: Cerebrolysin for vascular dementia

Comparison: 5 Sensitivity analyses

Outcome: 5 The improvement of global function reported as responder rates

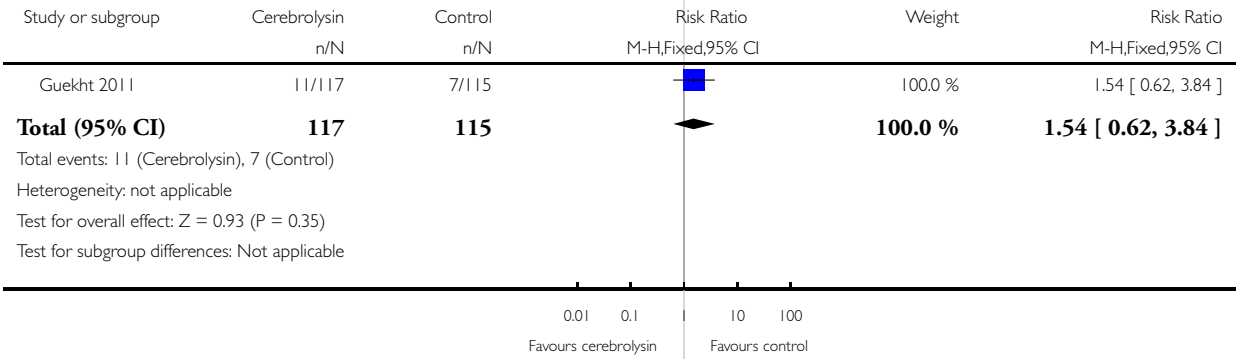


Analysis 5.6. Comparison 5 Sensitivity analyses, Outcome 6 Non-serious adverse events.

Review: Cerebrolysin for vascular dementia

Comparison: 5 Sensitivity analyses

Outcome: 6 Non-serious adverse events



APPENDICES

Appendix 1. Search November 2012

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Keyword search: cerebrolysin OR cere OR FPF1070 OR FPF (all dates)	19
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. cerebrolysin*.mp. 2. CERE.mp. 3. "FPF 1070".mp. 4. or/1-3 5. Dementia, Vascular/ 6. Dementia, Multi-Infarct/ 7. Delirium, Dementia, Amnestic, Cognitive Disorders/ or Dementia/ 8. Alzheimer Disease/ 9. Cerebrovascular Disorders/ 10. CADASIL/ 11. "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy".mp 12. dement*.mp. 13. alzheimer*.mp. 14. or/5-13 15. 4 and 14 16. randomized controlled trial.pt. 17. controlled clinical trial.pt. 18. randomi?ed.ab. 19. placebo.ab. 20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab. 24. or/16-23 25. (animals not (humans and animals)).sh. 26. 24 not 25 27. 15 and 26 28. (2011* or 2012*).ed. 29. 27 and 28	13
3. EMBASE 1980-2012 November 02 (Ovid SP)	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/	18

(*Continued*)

	6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp. 10. (chronic adj2 cerebrovascular).mp. 11. ("organic brain disease" or "organic brain syndrome").mp 12. "supranuclear palsy".mp. 13. ("normal pressure hydrocephalus" and "shunt*").mp. 14. "benign senescent forgetfulness".mp. 15. (cerebr* adj2 deteriorat*).mp. 16. (cerebral* adj2 insufficient*).mp. 17. (pick* adj2 disease).mp. 18. (creutzfeldt or jcd or cjd).mp. 19. huntington*.mp. 20. binswanger*.mp. 21. korsako*.mp. 22. CADASIL.mp. 23. or/1-22 24. cerebrolysin*.ti,ab. 25. CERE.mp. 26. "FPF 1070".mp. 27. FPF1070.ti,ab. 28. or/24-27 29. 23 and 28 30. random*.ti,ab. 31. trial*.ti,ab. 32. randomized controlled trial/ 33. controlled clinical trial/ 34. placebo.ti,ab. 35. "control group".ab. 36. ("double-blind*" or "double-mask*" or "single-blind*" or "single-mask*" or "triple-blind*" or "triple-mask*").ti,ab 37. or/30-36 38. 29 and 37 39. (2011* or 2012*).em. 40. 38 and 39	
4. PsycINFO 1806-October week 5 2012 (Ovid SP)	1. exp Dementia/ 2. exp Delirium/ 3. exp Huntingtons Disease/ 4. exp Kluver Bucy Syndrome/ 5. exp Wernickes Syndrome/ 6. exp Cognitive Impairment/ 7. dement*.mp. 8. alzheimer*.mp. 9. (lewy* adj2 bod*).mp.	11

(*Continued*)

	10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp. 16. (cerebr* adj2 deteriorat*).mp. 17. (cerebral* adj2 insufficient*).mp. 18. (pick* adj2 disease).mp. 19. (creutzfeldt or jcd or cjd).mp. 20. huntington*.mp. 21. binswanger*.mp. 22. korsako*.mp. 23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 24. or/1-23 25. cerebrolysin*.ti,ab. 26. CERE.mp. 27. "FPF 1070".mp. 28. FPF1070.ti,ab. 29. or/25-28 30. 24 and 29 31. (2011* or 2012*).up. 32. 30 and 31	
5. CINAHL (EBSCOhost)	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger*	2

(*Continued*)

	S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 TX cerebrolysin* S21 TX CERE S22 TX "FPF 1070" S23 TX FPF1070 S24 S20 or S21 or S22 or S23 S25 S19 and S24 S26 EM 2011 S27 EM 2012 S28 S26 OR S27 S29 S28 AND S25	
6. ISI Web of Knowledge [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports] - **BIOSIS Previews NOT searched**	Topic=(cerebrolysin* OR "FPF 1070" OR FPF1070) AND Topic=(dement* OR VaD OR "vascular cognitive impairment" OR VCI OR CADASIL OR cerebrovascular OR "subcortical VaD") AND Year Published=(2011-2012) Timespan=All Years. Search language=English Lemmatization=On	16
7. LILACS (BIREME)	cerebrolysin OR FPF1070 OR CERE OR FPF [Words]	11
8. CENTRAL (*The Cochrane Library*) (Issue 8 of 12, 2011)	#1 cerebrolysin* OR CERE OR "FPF 1070" OR FPF1070 #2 dement* #3 VaD #4 "vascular cognit*" OR VCI #5 CADASIL #6 cerebrovascular #7 (#2 OR #3 OR #4 OR #5 OR #6) #8 (#1 AND #7) [limit to 2011-2012]	2
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Interventional Studies | cerebrolysin OR CERE OR FPF1070 [rec:01/01/2011-11/04/2012]	2
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German	Interventional Studies | cerebrolysin OR CERE OR FPF1070 AND (dementia OR vascular) AND [rec:01/01/2011-04/11/2012]	2

(*Continued*)

Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]		
TOTAL before de-duplication		96
TOTAL after de-dupe and first-assess		25

Appendix 2. Search February 2011

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Advanced search: study design: RCT AND Intervention (contains any word): cerebrolysin cere FPF1070 FPF	20
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. cerebrolysin*.mp. 2. CERE.mp. 3. "FPF 1070".mp. 4. or/1-3 5. Dementia, Vascular/ 6. Dementia, Multi-Infarct/ 7. Delirium, Dementia, Amnestic, Cognitive Disorders/ or Dementia/ 8. Alzheimer Disease/ 9. Cerebrovascular Disorders/ 10. CADASIL/ 11. "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy".mp 12. dement*.mp. 13. alzheimer*.mp. 14. or/5-13 15. 4 and 14 16. randomized controlled trial.pt. 17. controlled clinical trial.pt. 18. randomi?ed.ab. 19. placebo.ab. 20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab.	51

(*Continued*)

	24. or/16-23 25. (animals not (humans and animals)).sh. 26. 24 not 25 27. 15 and 26	
3. EMBASE 1980-2011 week 7 (Ovid SP)	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/ 6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp. 10. (chronic adj2 cerebrovascular).mp. 11. ("organic brain disease" or "organic brain syndrome").mp 12. "supranuclear palsy".mp. 13. ("normal pressure hydrocephalus" and "shunt*").mp. 14. "benign senescent forgetfulness".mp. 15. (cerebr* adj2 deteriorat*).mp. 16. (cerebral* adj2 insufficient*).mp. 17. (pick* adj2 disease).mp. 18. (creutzfeldt or jcd or cjd).mp. 19. huntington*.mp. 20. binswanger*.mp. 21. korsako*.mp. 22. CADASIL.mp. 23. or/1-22 24. cerebrolysin*.ti,ab. 25. CERE.mp. 26. "FPF 1070".mp. 27. FPF1070.ti,ab. 28. or/24-27 29. 23 and 28 30. random*.ti,ab. 31. trial*.ti,ab. 32. randomized controlled trial/ 33. controlled clinical trial/ 34. placebo.ti,ab. 35. "control group".ab. 36. ("double-blind*" or "double-mask*" or "single-blind*" or "single-mask*" or "triple-blind*" or "triple-mask*").ti,ab 37. or/30-36 38. 29 and 37	69

(*Continued*)

4. PsycINFO 1806-February week 3 2011 (Ovid SP)	1. exp Dementia/ 2. exp Delirium/ 3. exp Huntingtons Disease/ 4. exp Kluver Bucy Syndrome/ 5. exp Wernickes Syndrome/ 6. exp Cognitive Impairment/ 7. dement*.mp. 8. alzheimer*.mp. 9. (lewy* adj2 bod*).mp. 10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp. 16. (cerebr* adj2 deteriorat*).mp. 17. (cerebral* adj2 insufficient*).mp. 18. (pick* adj2 disease).mp. 19. (creutzfeldt or jcd or cjd).mp. 20. huntington*.mp. 21. binswanger*.mp. 22. korsako*.mp. 23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 24. or/1-23 25. cerebrolysin*.ti,ab. 26. CERE.mp. 27. "FPF 1070".mp. 28. FPF1070.ti,ab. 29. or/25-28 30. 24 and 29	15
5. CINAHL (EBSCOhost)	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*"	5

(*Continued*)

	S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 TX cerebrolysin* S21 TX CERE S22 TX "FPF 1070" S23 TX FPF1070 S24 S20 or S21 or S22 or S23 S25 S19 and S24	
6. ISI Web of Knowledge - all databases [includes: Web of Science (1945-present) ; BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]	#1 Topic=(cerebrolysin* OR "FPF 1070" OR FPF1070) #2 Topic=(dement* OR VaD OR "vascular cognitive impairment" OR VCI OR CADASIL OR cerebrovascular OR "subcortical VaD") #3 #2 AND #1	100
7. LILACS (BIREME)	cerebrolysin OR FPF1070 OR CERE OR FPF	9
8. CENTRAL (*The Cochrane Library*) (Issue 4 of 4, Oct 2010)	#1 cerebrolysin* OR CERE OR "FPF 1070" OR FPF1070 #2 dement* #3 VaD #4 "vascular cognit*" OR VCI #5 CADASIL #6 cerebrovascular #7 (#2 OR #3 OR #4 OR #5 OR #6) #8 (#1 AND #7)	43
9. Clinicaltrials.gov (www.clinicaltrials.gov)	Interventional Studies | cerebrolysin OR CERE OR FPF1070	10
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry	cerebrolysin OR CERE OR FPF1070	11

(*Continued*)

of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]		
TOTAL before de-duplication		333
TOTAL after de-dupe and first-assess		127

CONTRIBUTIONS OF AUTHORS

Ning Chen and Mi Yang selected studies, extracted data, and assessed the methodological quality. Ning Chen and Cairong Zhu carried out analyses. Jian Guo and Muke Zhou helped to perform the bibliographic searches and carry out the analyses. Ning Chen produced the draft of the review. Li He, the corresponding author, developed the proposal, offered expert advice, reviewed the protocol, and is responsible for developing and updating the review.

DECLARATIONS OF INTEREST

Ning Chen - none known.

Mi Yang - none known.

Cairong Zhu - none known.

Jian Guo - none known.

Muke Zhou - none known.

Li He - none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we intended to perform separate meta-analyses using different periods of follow-up to avoid the unit of analysis error. However, in consideration of the various follow-up periods and small number of included trials, in the review we used final time-point data from each trial and, in the presence of any evidence of heterogeneity, analyzed subgroups based on treatment duration.