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Cerebrolysin for acute ischaemic stroke (Review)

Ziganshina LE, Abakumova T

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Cerebrolysin for acute ischaemic stroke.
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[Intervention Review]

Cerebrolysin for acute ischaemic stroke

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ABSTRACT

Background

Cerebrolysin is a mixture of low-molecular-weight peptides and amino acids derived from pigs' brain tissue, which has potential neuroprotective and neurotrophic properties. It is widely used in the treatment of acute ischaemic stroke in Russia, China, and other Asian and post-Soviet countries.

Objectives

To assess the benefits and risks of Cerebrolysin for treating acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (October 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (November 2014), MEDLINE (1966 to November 2014), EMBASE (1974 to November 2014), Web of Science Core Collection, with Science Citation Index (1940 to November 2014), LILACS (1982 to December 2014), OpenGrey (1980 to December 2014), and a number of Russian Databases (1998 to December 2014). We also searched reference lists, ongoing trials registers and conference proceedings, and contacted the manufacturer of Cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma).

Selection criteria

Randomised controlled trials comparing Cerebrolysin started within 48 hours of stroke onset and continued for at least two weeks with placebo or no treatment in people with acute ischaemic stroke.

Data collection and analysis

Two review authors independently applied inclusion criteria, assessed trial quality and risk of bias, and extracted data.

Main results

We included one trial involving 146 participants. We evaluated risk of bias and judged it to be high for generation of allocation sequence, low for allocation concealment, high for incomplete outcome data (attrition bias), unclear for blinding, high for selective reporting and high for other sources of bias. The manufacturer of Cerebrolysin, pharmaceutical company Ebewe, provided Cerebrolysin and the placebo, as well as the randomisation codes. There was no difference in the number of deaths (6/78 in Cerebrolysin group versus 6/68 in placebo group; risk ratio (RR) 0.87, 95% confidence interval (CI) 0.29 to 2.58) or in the total number of adverse events (16.4% versus 10.3%; RR 1.62, 95% CI 0.69 to 3.82) between the treatment and control groups.

Authors' conclusions

Routine administration of Cerebrolysin to people with acute ischaemic stroke cannot be supported by the available evidence from RCTs.

PLAIN LANGUAGE SUMMARY

Cerebrolysin for acute ischaemic stroke

Review question

Are there any benefits of using Cerebrolysin to treat people with acute ischaemic stroke, and are there any risks?

Background

Cerebrolysin, a mixture derived from pig brain tissue, is widely used in Russia, China, and other Asian and post-Soviet countries. We assessed evidence from randomised controlled trials (RCTs) investigating Cerebrolysin in people with acute ischaemic stroke.

Study characteristics

We included one RCT performed in eight centres in Austria, Hungary, and the Czech Republic. The trial compared Cerebrolysin with placebo in people with acute ischaemic stroke. Cerebrolysin was started within 24 hours of stroke onset and continued for 21 days as a once-daily intravenous infusion of 50 mL. The average age of the trial participants was 65 years; they were followed up for 90 days in total. The trial was supported by the manufacturer of Cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma).

Key results

The evidence is current up to November 2014. This review of one trial showed no beneficial effect of Cerebrolysin in acute ischaemic stroke. No significant increase in adverse effects was reported although they were more common in the Cerebrolysin group.

Quality of the evidence

The medication and methodology of the trial were provided by the manufacturer of Cerebrolysin creating a likely conflict of interest. There is very low quality evidence currently available that suggest Cerebrolysin performs no better than placebo in treating people with acute ischaemic stroke.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Cerebrolysin versus placebo in people with acute ischaemic stroke

Patient or population: people with acute ischaemic stroke
Settings: inpatient health facilities
Intervention: Cerebrolysin
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Cerebrolysin				
All-cause death	88 per 1000	77 per 1000 (26 to 228)	RR 0.87 (0.29 to 2.58)	146 (1 RCT)	⊕◯◯◯ Very low[1,2,3,4,5]	-
	88 per 1000	77 per 1000 (26 to 228)				
Total number of adverse events	103 per 1000	167 per 1000 (71 to 393)	RR 1.62 (0.69 to 3.82)	146 (1 RCT)	⊕◯◯◯ Very low[1,2,4,5,6]	-
	103 per 1000	167 per 1000 (71 to 393)				
Death or dependence at the end of the follow-up period	-	-	-	(0 trials)	-	Not reported
Early death (within 2 weeks of stroke onset)	-	-	-	(0 trials)	-	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Downgraded by one for risk of bias. 25/146 (17%) of trial participants were lost to follow-up. Trial authors did not report on time of death. The manufacturer of Cerebrolysin provided the medication and randomisation codes (procedure).

[2]No information on funding sources for the trial. No conflict of interest statement provided.

[3]Downgraded by one for imprecision. This single trial is underpowered to detect difference. The result was not statistically significant. Twelve deaths were reported, six in each group. Of these six were due to cerebral infarction: 4 in Cerebrolysin group, 2 in placebo group.

[4]Downgraded by one for inconsistency. This is the only eligible trial.

[5]Downgraded by one for indirectness. This single trial was conducted in the Czech Republic, Hungary, and Austria. The results may not be generalisable to other populations and situations.

[6]Downgraded by one for imprecision. This single trial is underpowered to detect rare but important adverse effects. The adverse events, except for the 12 deaths, are described as hypertension and constipation.

BACKGROUND

Effective, simple, and reliable treatment methods are urgently needed to decrease stroke mortality and disability. Many clinical trials and Cochrane reviews have addressed the question of benefits and risks of potential pharmacological treatment options for acute ischaemic stroke. However, strategies with proven therapeutic effects and an acceptable benefit-to-risk ratio are still lacking. Potential strategies can be grouped according to the existing evidence of their benefits and harms determining their role in clinical practice.

Evidence of benefit

Aspirin at a dose of 160 mg to 300 mg daily (orally or per rectum) started within 48 hours of onset of presumed ischaemic stroke appears to be the only effective treatment for early secondary prevention, reducing the risk of early recurrent ischaemic stroke without a major risk of early haemorrhagic complications and improving long-term outcomes (Sandercock 2014). Despite the positive overall conclusions of a Cochrane review of thrombolysis in acute ischaemic stroke (Wardlaw 2014) and individual patient data meta-analysis (Emberson 2014), the dispute on the timing of the use of intravenous recombinant tissue plasminogen activators (rtPA) is still ongoing (Alper 2015). It is estimated that for each patient with a good stroke outcome at six months, another patient would have symptomatic intracranial bleeding, and for every three to four patients without neurological deficits at six months, there is an excess of one patient death after thrombolysis (Appelros 2015; Brunström 2015). The evidence is inadequate to conclude whether lower doses of thrombolytic agents are more effective than higher doses, whether one agent is better than another, or which route of administration is the best for treatment of people who have had an acute ischaemic stroke (Wardlaw 2013).

Evidence of harm

Glycoprotein IIb-IIIa inhibitors (abciximab and tirofiban) increase the risk of intracranial haemorrhage without evidence of any reduction in death or disability in stroke survivors (Ciccone 2014). These data do not support their routine use in clinical practice. Abciximab contributed 89% of the total number of participants of the Cochrane review (Ciccone 2014). Anticoagulants (standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors) as immediate therapy for acute ischaemic stroke are not associated with net short- or long-term benefit. Reduced rate of recurrent stroke, deep vein thrombosis, and pulmonary embolism with anticoagulant therapy was offset by the increased risk of intracranial haemorrhage and extracranial bleeding. The data do not support the routine use of any the currently available anticoagulants in acute ischaemic stroke (Berge 2002; Sandercock 2008a; Sandercock 2008b). Long-term anticoagulant therapy in people with presumed non-cardioembolic ischaemic stroke or transient ischaemic attack was not associated with any benefit, but there was a significant bleeding risk (Sandercock 2009).

Tirilazad, an amino steroid inhibitor of lipid peroxidation, increased the combined end-point of 'death or disability' in people with acute ischaemic stroke (TISC 2001). Lubeluzole, an ion channel modulator of glutamate release that has a benzothiazole structure with potential neuroprotective properties, did not reduce death or dependency in acute ischaemic stroke patients. In contrast, it increased heart-conduction disorders (Q-T prolongation) (Gandolfo 2002).

Evidence of lack of benefit

The evidence of the lack of benefit have accumulated for the following treatment options, which were tested in clinical trials and the results of which were systematically reviewed: corticosteroids (Sandercock 2011); calcium antagonists (Horn 2000); haemodilution (Chang 2014); excitatory amino acid antagonists, including ion channel modulators and N-methyl-D-aspartic acid (NMDA) antagonists (Muir 2003); piracetam (Ricci 2012a); and a free radical trapping agent NXY-059 (Shuaib 2007).

Role in clinical practice

There is still inadequate evidence from RCTs for the following antithrombotic agents: oral antiplatelet drugs other than aspirin (clopidogrel, ticlopidine, cilostazol, satigrel, sarpolgrelate, KBT 3022, iisbogrel) (Sandercock 2014); and fibrinogen-depleting agents (ancrod and defibrase) (Hao 2012).

The longest list of interventions is that of agents tested in clinical trials with subsequent Cochrane reviews of results that documented inadequate evidence to establish a role in clinical practice and includes: ginkgo biloba (Zeng 2005); percutaneous vascular interventions, including intra-arterial thrombolysis with urokinase and pro-urokinase (O'Rourke 2010); sonothrombolysis (Ricci 2012b); glycerol (Righetti 2004); naftidrofuryl, a 5-HT2 serotonergic antagonist (Leonardi-Bee 2007); theophylline or methylxanthine derivatives (Bath 2004a; Bath 2004b); mannitol (Bereczki 2007); nitric oxide donors (Bath 2002); blood pressure altering (BASC 2000; BASC 2001); prostacyclin and its analogues (Bath 2004c); vinpocetine (Bereczki 2008); and gangliosides (Candelise 2001); Chinese herbal medicine Sanchi (Chen 2008), puerarin (Tan 2008), mailuoning (Yang 2009), and the neuroprotective agent edaravone (Feng 2011), which are widely used for ischaemic stroke in China. Cerebrolysin belongs to this category (Ziganshina 2010a).

Description of the condition

Ischaemic stroke occurs when the brain loses its blood and energy supply, resulting in damage to brain tissue; it is a brain equivalent of a heart attack. Most strokes (87%) are ischaemic (AHA 2014). Worldwide every year 15 million people suffer a stroke: five and a half million people die and another five million are left permanently disabled, placing a burden on family and community (WHO 2014). Stroke is one of the major causes of disability and mortality (AHA 2014; WHO 2014; Bonita 1992). It is the third most common cause of death in the developed world after coronary disease and cancer. The World Health Organization (WHO) stroke statistics registered the number of deaths from stroke to be more than 200,000 in the Russian Federation, as well as in China and in India, with the highest number of 1,652,885 in China and 517,424 in Russia in 2002 (WHO 2014). According to the Russian data there are between 400,000 to 450,000 cases of acute stroke registered in the Russian Federation annually (Gusev 2003) with the incidence of 3.36 per 1000 population and standardised incidence of 2.39 (3.24 in men and 2.24 in women) per 1000 population (Gusev 2013). The stroke mortality rate is 40.37% (61.4% for haemorrhagic stroke and 21.8% for ischaemic stroke). The north-west regions had the highest stroke incidence of 7.43 per 1000, followed by some cities in middle areas of the country (5.37 per 1000) and the far east (4.41 per 1000) (Gusev 2003; Vilenski 2006b). The stroke recurrence rate is 30% (Suslina 2009). Stroke survivors experience serious neurological disorders (loss of vision, speech or both, paralysis, and confusion) and these are not restored in 30% to 66% of cases six months after a stroke (French 2007). In Russia, stroke is the number one cause of disability in adults - 32 cases per 100,000 population. By the end of one year 25% to 30% of stroke survivors develop dementia. Stroke presents a huge financial burden for the health system (Martynchik 2013).

Description of the intervention

Cerebrolysin is a mixture of low-molecular-weight peptides and amino acids derived from pigs' brain tissue, which has potential neuroprotective and neurotrophic properties. Its manufacturer promotes it for multiple neurological conditions, and it is widely used in the treatment of acute ischaemic stroke in Russia, China, and other Asian and post-Soviet countries.

How the intervention might work

The term 'neuroprotection' is used to describe the putative effect of interventions protecting the brain from pathological damage. In ischaemic stroke the concept of neuroprotection includes inhibition of pathological molecular events leading to calcium influx, activation of free radical reactions and cell death. Knowledge of pathophysiology in acute ischaemic stroke stimulated development of a number of potential neuroprotective agents. Many neuroprotective agents have proven to be efficacious in animal studies. However, demonstration of benefit in people with acute ischaemic stroke on clinically relevant outcomes has not been successful. Cerebrolysin is a mixture of low-molecular-weight peptides (80%) and free amino acids (20%) derived from pig brain tissue, with proposed neuroprotective and neurotrophic properties similar to naturally occurring growth factors (nerve growth factor, brain-derived neurotrophic factor) (Alvarez 2000; Fragoso 2002).

Results of in vitro and animal studies of Cerebrolysin have been traditionally used to suggest its potential for treating acute ischaemic neuronal damage (Masliah 2012). For example, Cerebrolysin was shown to be effective in tissue culture models of neuronal ischaemia dose-dependently increasing neuronal survival (Schauer 2006). In brain slices it counteracted necrotic and apoptotic cell death induced by glutamate (Riley 2006). Cerebrolysin also demonstrated neuroprotective activity in a rat model of haemorrhagic (Makarenko 2005) and ischaemic stroke (Zhang 2010), as well as spinal cord trauma (Sapronov 2005). One randomised double blind placebo-controlled trial showed no effect of Cerebrolysin in acute haemorrhagic stroke on chosen efficacy measures (Barthel Index (BI), Unified Neurological Stroke Scale, and Syndrome Short Test (SST)) (Bajenaru 2010).

Why it is important to do this review

Despite the effectiveness of neuroprotective agents in animal models of stroke, clinical trials of neuroprotective agents in humans have provided disappointing results (European Ad Hoc Consensus 1998). More recent Cochrane reviews of the effects of individual neuroprotective agents and pharmacological groups confirmed have this (Gandolfo 2002; Muir 2003; Ricci 2012a; TISC 2001). Other means of neuroprotection are being sought. Cerebrolysin is well accepted by Russian and Asian physicians. It is widely used in the treatment of acute ischaemic stroke and other neurological disorders (Chukanova 2005; Gromova 2006; Onishchenko 2006). Research data from observational studies and clinical trials of Cerebrolysin in acute stroke or head injury, with most performed in Russia and China, have accumulated (Chukanova 2005; Gafurov 2004; Gromova 2006; Ladurner 2005; Skvortsova 2004; Skvortsova 2006; Skvortsova 2008; Wong 2005). We carried out a Cochrane systematic review, which did not find sufficient evidence to support Cerebrolysin use in practice (Ziganshina 2010a). Cerebrolysin, as assessed in a Cochrane systematic review for vascular dementia, may have positive effects on cognitive function and global function in elderly people with mild to moderate dementia, but the review authors do not recommend it for routine use in vascular dementia due to the limitations of the studies and the resulting review: small number of included trials, wide variety of treatment durations, and short-term follow-up (Chen 2013b). Cerebrolysin has also been proposed for treatment of people with Alzheimer's disease (Fragoso 2002). Trials of Cerebrolysin in acute haemorrhagic stroke have been assessed in a meta-analysis (Shu

2012), concluding on its safety and supporting implementation of new trials for definitive efficacy assessment.

The previous version of this Cochrane review, based on one eligible trial only, did not find evidence of Cerebrolysin benefit in acute ischaemic stroke (Ziganshina 2010a). Since then more research data from clinical trials of Cerebrolysin in acute ischaemic stroke have become available, which requires an update of this systematic review to evaluate these new results.

The aim of this Cochrane review is to verify whether the available evidence from controlled trials is in favour of a beneficial effect of Cerebrolysin for acute ischaemic stroke.

OBJECTIVES

To assess the benefits and risks of Cerebrolysin for treating acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs), published or unpublished, comparing Cerebrolysin with placebo or no treatment in people with acute ischaemic stroke. We excluded uncontrolled studies, as well as quasi-RCTs where allocation to treatment or control was not concealed (e.g. allocation by alteration, open random number list, date of birth, day of the week, or hospital number).

Types of participants

People with acute ischaemic stroke, irrespective of age, gender, or social status, whose symptom onset was less than 48 hours previously. Stroke symptoms include: sudden weakness or numbness of the face, arm, or leg, often unilateral; confusion; difficulties in speaking or seeing with one or both eyes; difficulties walking; loss of balance or co-ordination; severe no-cause headache; fainting or loss of consciousness. Stroke diagnosis confirmation with neuroimaging was not a required eligibility criterion.

Types of interventions

We planned to compare Cerebrolysin or newer peptide-mixtures, which we have named 'Cerebrolysin-like agents', with placebo or no treatment. We also planned to compare Cerebrolysin or Cerebrolysin-like agents added to standard treatment versus standard treatment alone. Standard treatment is not defined precisely and may differ between studies. Study medication must have been started within 48 hours of stroke onset and must have continued for at least two weeks. If trials of Cerebrolysin versus other neuroprotective agents are identified in future we will add a separate analysis for this comparison.

Types of outcome measures

Primary outcomes

1. Poor functional outcome defined as death or dependence at the end of the follow-up period.
2. Early death (within two weeks of stroke onset).

Secondary outcomes

1. Quality of life, if assessed in the included studies.
2. All-cause death.
3. Time to restoration of capacity for work.

Adverse events and effects

1. Serious adverse events: fatal, life threatening, requiring hospitalisation or change of treatment regimen.
2. Adverse effects specifically associated with Cerebrolysin, such as hypersensitivity reactions.
3. Total number of adverse events.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We attempted to identify all relevant trials regardless of language or publication status, and arranged translation of relevant papers published in languages other than English.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (October 2014); the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, November 2014) (Appendix 1); MEDLINE (1966 to November 2014) (Appendix 2); EMBASE (1974 to November 2014) (Appendix 3); Web of Science Core Collection, which includes Science Citation Index (1940 to November 2014) (Appendix 4); LILACS (Latin American and Caribbean Health Sciences Literature) (1982 to December 2014) (Appendix 5); OpenGrey (System for Information on Grey Literature in Europe) (http://www.opengrey.eu) (1980 to December 2014) (Appendix 6); and the following Russian Databases: e-library (http://elibrary.ru (1998 to December 2014); and East-View (http://online.ebiblioteka.ru/index.jsp) (2006 to December 2014) (Appendix 7).

We also searched the following ongoing trials and research registers (December 2014): the Stroke

Trials Registry (http://www.strokecenter.org/trials/), ClinicalTrials.gov (http://clinicaltrials.gov/), and ISRCTN Registry (http://www.isrctn.com).

The Cochrane Stroke Group Information Specialist Brenda Thomas developed the search strategies for CENTRAL, MEDLINE, EMBASE, and Web of Science and we adapted the MEDLINE strategy for the other databases.

Searching other resources

In an effort to identify further published, unpublished, and ongoing trials and obtain additional trial information we:

1. checked the reference lists of all trials identified by the above methods;
2. searched the following neurology conference proceedings held in Russia: Chelovek i Lekarstvo (2006 to 2014), National'niy congress cardiologov (2006 to 2014), Rossiyskiy Mezhdunarodniy Congress Cerebrovascularnaya patologiya i insult (2008 to 2014);
3. contacted the manufacturer of Cerebrolysin, pharmaceutical company EVER Neuro Pharma GmbH (formerly Ebewe Pharma) (December 2014).

Data collection and analysis

Selection of studies

Two review authors (LEZ and TRA) independently examined titles and abstracts of records from the electronic searches and excluded obviously irrelevant studies. We obtained the full text of the remaining papers and the same two authors independently selected studies for inclusion based on the pre-determined inclusion criteria. We resolved disagreements through discussion. We excluded studies that did not meet the inclusion criteria and gave the reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (LEZ and TRA) independently extracted data using a standardised data extraction form. We extracted data on the methods of the studies, participants, interventions, and outcomes. We resolved any differences in the extracted data by referring to the original articles and through discussion. We extracted data to allow an intention-to-treat (ITT) analysis (including all the participants in the groups to which they were originally randomly allocated) and we presented the data in the Characteristics of included studies table. We calculated the percentage loss to follow-up and presented it in the 'Risk of bias' table.

For binary outcomes, we extracted the number of participants with the event in each group. For continuous outcomes, we planned to use arithmetic means and standard deviations for each group.

Assessment of risk of bias in included studies

We (LEZ and TRA) independently evaluated methodological quality in terms of generation of allocation sequence, allocation concealment, blinding, loss to follow-up of participants, and other risks of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011).

We followed the guidance to assess whether adequate steps had been taken to reduce the risk of bias across six domains: generation of allocation sequence; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. We have categorized these judgments as 'low', 'high', or 'unclear' risk of bias. Where we judged risk of bias as unclear, we attempted to contact the trial authors for clarification. We considered loss to follow-up to be acceptable if it was less than 10%. We resolved any disagreements arising at any stage by discussion.

Measures of treatment effect

We presented dichotomous data and we combined them using risk ratios (RRs). We showed RRs accompanied by 95% confidence intervals (CIs).

Unit of analysis issues

We did not have any unit of analysis issues.

Dealing with missing data

We undertook analysis according to the ITT principle. Where the number of people with a measured outcome was not reported, we extracted the number of participants and performed an ITT analysis. We used the data on the number of deaths in both groups to generate the secondary outcome of all-cause death and we used the number of people randomised into each comparison group as the denominator.

Assessment of heterogeneity

We planned to test for homogeneity or heterogeneity of effect sizes between studies using the I^2 statistic, with a value of 50% used to denote moderate levels of heterogeneity.

Assessment of reporting biases

We planned to use funnel plots to examine asymmetry that may have been caused by publication bias or heterogeneity. However, we could not do this due to the lack of eligible studies.

Data synthesis

We undertook analysis according to the ITT principle. We used RevMan 2014 to analyse the data. We used RR as a measure of effect for binary outcomes. For continuous data, we planned to use

the mean difference (MD). If appropriate, we planned to calculate a summary statistic for each outcome.

Subgroup analysis and investigation of heterogeneity

We planned to investigate potential sources of heterogeneity using the following subgroups, if the number of studies permitted:

1. Cerebrolysin dose;
2. length of treatment.

Where it was appropriate to pool data and heterogeneity was detected, we planned to use the random-effects model.

Sensitivity analysis

We planned to perform a sensitivity analysis to test the robustness of the results. We planned to investigate the effect of methodological study quality (low, moderate, or high risk of bias) using a sensitivity analysis.

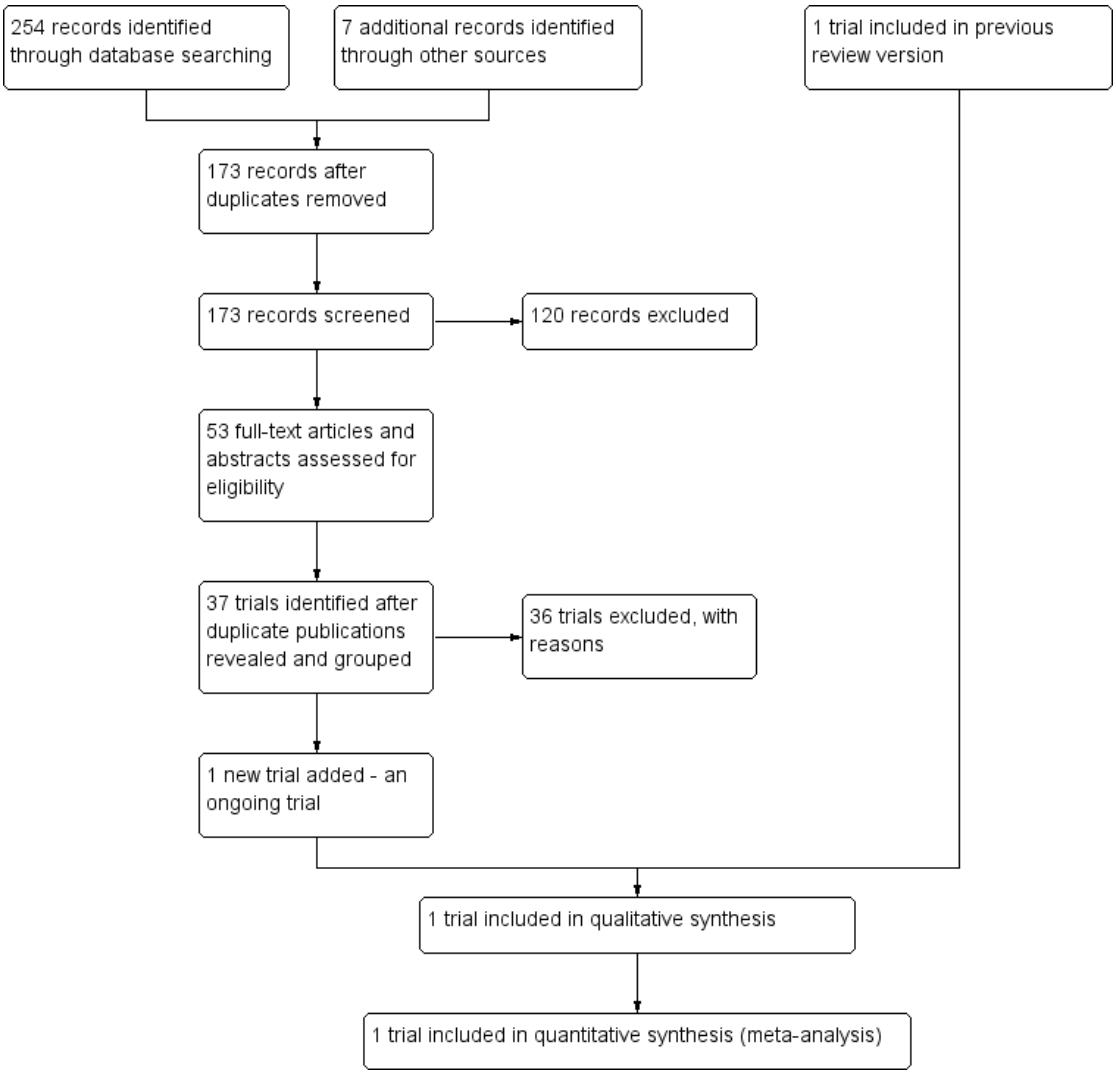
RESULTS

Description of studies

Results of the search

We identified 254 records through database searches and seven additional records from other sources. After removal of duplicates 173 records remained, which we screened and excluded 120 records. We retrieved 53 full-text articles and abstracts. After controlling for duplicate publications of the same trial we identified 37 trials and assessed them for eligibility as per protocol. We excluded 36 trials and identified two eligible trials. One was the same RCT included in the previous version of this review, Ziganshina 2010a (see 'Characteristics of included studies'). We categorised the other trial as ongoing (IRCT138803272042N1) as we did not find any published results (see 'Characteristics of ongoing studies'). We illustrated these results in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Only one trial met the inclusion criteria (Ladurner 2005). This was a multicentre placebo-controlled study conducted in Austria, the Czech Republic, and Hungary. It was supported by the manufacturer of Cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma). The trial described distinct inclusion and exclusion criteria. The average age of participants in the two comparison groups was 65 years. The trial randomised 146 participants within 24 hours of stroke onset to either the treatment group (Cerebrolysin plus basic therapy; 78 participants) or to the control group (placebo plus basic therapy; 68 participants). There were no significant differences between the two groups in terms of baseline characteristics. In the treatment group, Cerebrolysin was administered intravenously once a day in a dose of 50 mL over a period of 20 minutes for 21 days. Cerebrolysin was provided to the study centres by Ebewe Pharma. the placebo consisted of 100 mL normal saline. The same basic therapy was used in the treatment group and the control group (pentoxifylline and acetylsalicylic acid).
The outcome measures used were the Canadian Neurological Scale (CNS), the BI, the Glasgow Coma Scale (GCS), the Clinical Global Impression (CGI), the Mini-Mental State Examination (MMSE), the SST, the Self Assessment Scale, and the Hamilton Rating Scale for Depression (HAMD) - performed at baseline and

at subsequent visits on days one, three, seven, 14, 21, and 90. Adverse effects included abnormal laboratory findings and changes in clinical laboratory tests, changes in vital signs, and general physical and neurological examinations rated as mild, moderate, and severe. The numbers of participants who died during the study period in both the Cerebrolysin group and the placebo group were reported in the safety section of the paper. We used these numbers to assess all-cause death. The duration of follow-up was 90 days; 25 participants (17%) were lost to follow-up, nine of which were in the treatment group and the remaining 16 were in the control group. We have presented details of the included trial in the Characteristics of included studies table.
There are no trials awaiting assessment.

Excluded studies

We excluded 35 trials because:

1. outcomes reported were only either impairment scales or the number of participants with neurological improvement without any of the predefined outcome measures;
2. study medication was not started within 48 hours of stroke onset and had not been continued for at least 14 days;
3. research questions were not relevant;
4. studies used different comparisons; or
5. studies were reported as abstracts only.

We have presented the reasons for excluding these studies in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

Only one RCT met the inclusion criteria.

Allocation

The manufacturer of Cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma), provided the randomisation method: a computer-generated randomisation code. We judged this to be a source of high risk of bias for generation of the allocation sequence. For allocation concealment the trial authors used sealed envelopes with information on the actual treatment dispensed and provided them to the investigator for emergency cases. The published report described that all envelopes remained sealed throughout the study. Although the trial authors did not describe the envelopes as opaque, we judged the allocation concealment to be at low risk of bias.

Blinding

The trial authors reported that investigators and all study personnel were blinded. However, it was impossible to assess blinding by outcome.

Incomplete outcome data

Twenty-five participants out of 146 (17%) randomised were lost to follow-up. We judged this to be the source for the high risk of attrition bias.

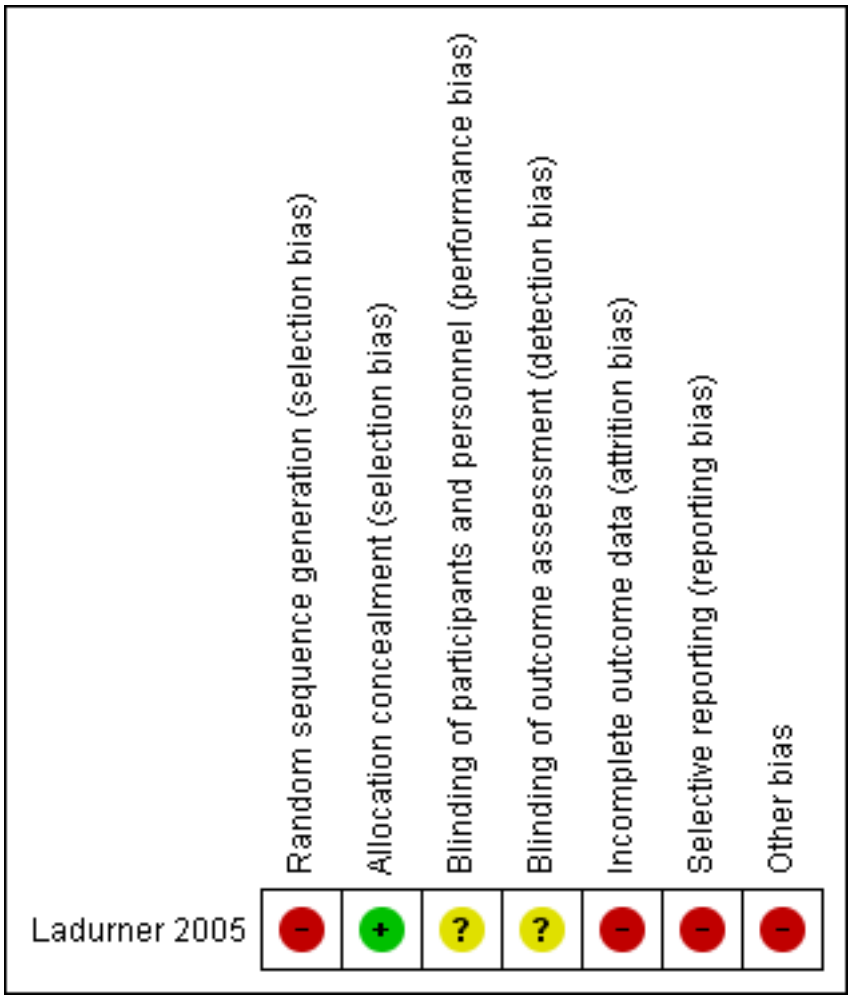
Selective reporting

We compared, by the ITT principle, the number of deaths extracted from the safety section of the trial report and presented data as all-cause death without performing any analysis (Ladurner 2005).

Other potential sources of bias

The manufacturer of Cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma), provided the study medication Cerebrolysin and the placebo, as well as the randomisation codes (procedure). Further involvement of the pharmaceutical company in the trial design, the execution of the trial, or in the analyses was not described in the published trial report. The trial authors did not provide any information on funding sources for the trial and report drafting. The trial report has no conflict of interest statement (Ladurner 2005). We have illustrated these judgements in the 'Risk of bias' summary plot (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Cerebrolysin versus placebo in people with acute ischaemic stroke

The included trial did not report on the primary outcome measures, such as poor functional outcome (defined as death or dependence at the end of the follow-up period) and early death (within two weeks of stroke onset). It did not report on any of the secondary outcome measures: quality of life, all-cause death, and time to restoration of capacity for work. We used the data on the number of deaths in both groups to generate the secondary outcome of all-cause death. Six participants (six of 78 randomised) died in the Cerebrolysin group and six participants died in the placebo group (six of 68 randomised). We calculated the RR for the extracted outcome all-cause death: RR 0.87, 95% CI 0.29 to 2.58 (Analysis 1.1). The trialists reported on the following causes of death: cerebral infarct (four in the Cerebrolysin group and two in the placebo group), heart failure (two in the Cerebrolysin group and one in the placebo group), pulmonary embolism (two in the placebo group), and pneumonia (one in the placebo group). The trial authors did not report on the time when those deaths occurred.

Adverse events and effects

The trial authors reported the overall incidence of adverse events: 16.4% in the Cerebrolysin group and 10.3% in the placebo group. We calculated the RR for the outcome total number of adverse events: RR 1.62, 95% CI 0.69 to 3.82 (Analysis 1.2). The trial authors reported only one serious non-fatal adverse event in the

placebo group: haematemesis. They did not report on any adverse effects specifically associated with Cerebrolysin, for example, hypersensitivity reactions.

Sensitivity analyses

As we only included one study, we did not perform the planned sensitivity analyses.

DISCUSSION

The WHO collection of National Essential Medicines Lists (EML) includes the latest acting country editions, which recommend Cerebrolysin for treating various neurological conditions, including acute ischaemic stroke. These include the National EMLs of the Russian Federation (GovRu 2015), Ukraine, and the Republic of Uzbekistan (WHO 2015).

However, the potential benefits of Cerebrolysin for improving clinical outcomes in patients with acute ischaemic stroke have not been proven in RCTs of acceptable quality.

In this Cochrane review we assessed the benefits and harms of Cerebrolysin when added to standard treatment for acute ischaemic stroke, focusing on clinically relevant and widely accepted outcomes, and specifically excluding assessment methods with numerous varying scales.

Summary of main results

The only included trial, supported by the manufacturer of Cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma), did not provide sufficient evidence of the effects of Cerebrolysin on clinically relevant outcome measures for acute ischaemic stroke, such as poor functional outcome (death or dependence by the end of the follow-up period) and early death (within two weeks of stroke onset).

In terms of all-cause death, Cerebrolysin performed no better than placebo.

Despite the lack of evidence of efficacy in acute ischaemic stroke Cerebrolysin is widely used in Russia, China, and other Asian countries.

Therefore, the routine use of Cerebrolysin in people with acute ischaemic stroke is not supported by any evidence from the existing clinical trials. Any further studies conducted in this area must be well-designed RCTs assessing clinical outcome measures rather than stroke scale parameters or other surrogate outcomes, such as infarct volume. The studies should be reported in full to allow the wider scientific community to gain a better understanding of the potential value or risks of Cerebrolysin in acute ischaemic stroke. The potential benefit of neuroprotection for clinical outcomes in acute ischaemic stroke needs to be reassessed.

Overall completeness and applicability of evidence

In this Cochrane review update, we restricted inclusion of trials, as per protocol, to those that recruited people with confirmed acute ischaemic stroke, for whom trialists initiated treatment within 48 hours of stroke onset. We also followed the protocol in restricting the review scope to trials in which the intervention, Cerebrolysin or placebo, was used for at least 14 days (two weeks).

In the only eligible trial, which was carried out in eight centres in Austria, Hungary, and the Czech Republic, the trial sets were not geographically diverse. However, there is a lack of eligible studies conducted in Asia. The included trial was conducted in middle-income and high-income countries, which means the results of this Cochrane review are likely to be applicable to settings where the burden of stroke and stroke deaths is high. However, it may not be applicable to settings of low-income countries, where the burden of stroke deaths and disability is even higher (WHO 2014) and poses huge financial demand on health systems and society (Martynchik 2013). Hence, new revised treatment strategies on the use of Cerebrolysin in acute stroke patients are most urgently needed. The only included trial did not test varying doses or treatment duration with Cerebrolysin. Given the poor prognosis of stroke patients, further evidence relating to the use of Cerebrolysin in conjunction with aspirin would be welcome. Within the only eligible trial, reporting of the selected outcomes was inconsistent and incomplete. The authors categorised their trial as an exploratory trial. Furthermore, reporting of data on death and safety parameters without clarification on the time of death and development of adverse events made meaningful interpretation of these data impossible. Harmonised reporting standards for these and other outcomes in stroke trials would be welcome, given that one ongoing trial was identified and may potentially expand the evidence base addressing the questions of this review. Given the exploratory nature of the included small study, the power of analysis of the only two reported clinically relevant efficacy and safety outcomes is bound to be limited.

The trial did not report on Cerebrolysin-specific adverse effects, such as hypersensitivity and emotional disturbances - arousal and aggression or fatigue, tiredness and apathy or sleeplessness, convulsive preparedness, rise or fall in blood pressure, shortness of breath, flu-like syndrome, reactions on immediate intravenous administration like feelings of chills or heat, cold sweat, dizziness and tachycardia, or redness and itching at the site of administration, gastrointestinal disturbances, and others (Registry of Medicines 2015).

However, the trial authors reported the total number of adverse events, including those that, according to the trial authors, led to the deaths of trial participants, and detected no difference.

Quality of the evidence

We assessed the quality of the evidence using the GRADE process (Guyatt 2008) and we presented the results in Summary of findings for the main comparison. For this table we asked the following question: should Cerebrolysin be used in acute ischaemic stroke to improve clinical outcomes? We do not know from this single trial (Ladurner 2005) whether or not Cerebrolysin in addition to standard first-line regimen improves treatment outcomes in people with confirmed ischaemic stroke. There is very low quality evidence that Cerebrolysin performs no worse than placebo in treating people with acute ischaemic stroke if started within 48 hours of stroke onset and continued for 21 days as once daily intravenous infusions of 50 mL Cerebrolysin (Summary of findings for the main comparison).

Potential biases in the review process

We performed the data extraction unblinded. The included trial is published and we were unable to obtain further unpublished data from the manufacturer of Cerebrolysin - EVER Neuro Pharma GmbH (formerly Ebewe Pharma).

Agreements and disagreements with other studies or reviews

We asked whether Cerebrolysin has a role in improving the treatment outcomes in people diagnosed with acute ischaemic stroke. The original version of this review provided evidence that Cerebrolysin performed no better than placebo (Ziganshina 2010a). These unfavourable results argue against its widespread use and its inclusion on national EMLs in Russia, Ukraine, and Uzbekistan. As new research data has accumulated, we have updated the review, having performed new literature searches. The conclusions have not been changed by the results of this updated Cochrane review.

In this review update, we did not find any evidence to support Cerebrolysin use as a treatment option for acute ischaemic stroke. Estimates from the only eligible trial (Ladurner 2005) suggest that all-cause death is not improved with Cerebrolysin use compared with placebo, and reported numbers of adverse events were not statistically different.

The methodological quality of most clinical trials of Cerebrolysin is insufficient for inclusion in this Cochrane review. Notably, among the excluded studies, the Skvortsova 2004 trial of 10 mL and 50 mL Cerebrolysin versus placebo for 10 days in people in Russia reported no difference in all-cause death between Cerebrolysin and placebo by day 30 after stroke onset.

Another trial excluded from this review - a multicentre prospective controlled study of Cerebrolysin versus placebo in 277 patients with acute ischaemic stroke, performed in Russia by the same author team - showed a trend towards higher death rates in the Cerebrolysin group compared with the placebo group (seven versus one). The Cerebrolysin treatment regimen was 10 mL intravenously for 10 days (Skvortsova 2006). The study authors reported on the safety of Cerebrolysin use and its benefit for scales' indices.

A newer, larger multicentre trial including 1070 participants from China, Hong Kong, South Korea, and Myanmar, which was excluded from this review for not meeting the eligibility criteria for Cerebrolysin use (only 30 mL of Cerebrolysin was given for 10 days in addition to aspirin), found estimates of efficacy and safety outcomes to be similar for Cerebrolysin and placebo (CASTA 2012). There was no difference in death (28 and 32 in the Cerebrolysin and placebo groups respectively), described by the trial report authors in the safety section as fatal adverse events not related to the study drug. The number of serious non-fatal adverse events was 50 in the Cerebrolysin group and 39 in the placebo group. The manufacturer of Cerebrolysin provided funding support for the trial and 23% of participants (244/1069) were lost to follow-up. Thus this excluded trial had multiple risks of bias. However, it confirms the findings of this Cochrane review on the lack of benefits of Cerebrolysin for acute ischaemic stroke, although the quality of evidence is very low and the study authors' conclusions advocate for the safe use of Cerebrolysin in acute ischaemic stroke.

Another excluded trial tested Cerebrolysin or placebo combined with alteplase (Cerebrolysin 30 mL or placebo were administered one hour after thrombolytic treatment as a daily intravenous infusion given for 10 consecutive days) in 119 people with acute ischaemic hemispheric stroke in Austria and some eastern European countries (CERE-LYSE-1 2012). The trial did not find any benefits of adding Cerebrolysin to alteplase at 90 days of follow-up. Four patients died both in the Cerebrolysin group and the placebo group. Again, the study authors did not find any relationship to the study medication. Also, there were more participants with serious adverse events in the Cerebrolysin group than in the placebo group (12 versus seven). The study authors advocate for the safe use of Cerebrolysin in combination with alteplase.

From these examples we see that the published reports on Cerebrolysin use in people with acute ischaemic stroke advocate in their conclusions and abstracts that Cerebrolysin is safe and is well tolerated. Most reports reported on its beneficial changes in surrogate efficacy measurements and various stroke scales, which are reported inconsistently by investigators and not universally accepted. This has been reported despite the consistently higher numbers of deaths or people with serious adverse events in the Cerebrolysin groups. In all these excluded studies Cerebrolysin was used in smaller doses and for shorter periods of time, making them ineligible for inclusion.

Cerebrolysin may not be an acceptable treatment component for people with acute ischaemic stroke. It neither reduces stroke death rate nor has it been adequately tested for safety. We could not identify any clear evidence that Cerebrolysin can improve outcome after ischaemic stroke.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this Cochrane review do not demonstrate clinical benefits of Cerebrolysin for treating acute ischaemic stroke. We could not identify any reliable clinical evidence to support the routine use of Cerebrolysin in acute ischaemic stroke.

Implications for research

Future research, if any at all, should focus on well-designed RCTs to assess the effects of Cerebrolysin on clinical outcomes. The trial investigators must ensure that they use pragmatic clinical outcome measures including, as a minimum, early death, dependency, all-cause death, and adverse events, as well as treatment duration not less than 14 days. They must provide a detailed description of any basic or routine therapy used concurrently with Cerebrolysin (these should be the same in both the intervention and control groups). The trials should be reported in full and conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher 2001).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ladurner 2005

Methods	Multicentre, randomised, double-blind controlled trial 25 participants (17%) were lost to follow-up Mean duration of follow-up: 90 days
Participants	146 participants randomised, 121 evaluated Inclusion criteria: men and women with their first acute ischaemic stroke with clinical symptoms of middle cerebral artery area, aged 45 to 85 years, admitted to hospital and started on medication within 24 hours after stroke onset, with a Glasgow Coma Score > 10 and a CNS score between 4.5 to 8.0 at baseline Exclusion criteria: haemorrhagic stroke, transient ischaemic attacks, uncontrollable hypertension, acute myocardial infarction, congestive heart failure, moderate to severe dementia prior to stroke, stupor or coma, severe concomitant diseases, impaired renal function, history of prior stroke
Interventions	Intervention: Cerebrolysin 50 mL (mixed with 50 mL normal saline) by intravenous infusion over 20 minutes for 21 days after admission to the hospital in addition to basic therapy (78 participants) Control: placebo (100 mL normal saline) by intravenous infusion over 20 minutes for 21 days after admission to hospital in addition to basic therapy (68 participants) Basic therapy: pentoxifylline (300 mg/day intravenously) and acetylsalicylic acid (250 mg/day orally) for the first 21 days; pentoxifylline (2 x 400 mg/day orally) and acetylsalicylic acid (250 mg/day orally) from day 22 to 90
Outcomes	1. Efficacy measures: Canadian Neurological Scale, Barthel Index, Glasgow Coma Scale, Clinical Global Impression, Mini-Mental State Examination, Syndrome Short Test, Self Assessment Scale, and the Hamilton Rating Scale for Depression performed at baseline and at all subsequent study visits on days 1, 3, 7, 14, 21, and 90 2. Adverse events, including abnormal laboratory findings and changes in clinical laboratory tests, changes in vital signs and general physical and neurological examinations rated as mild, moderate and severe 3. All-cause mortality reported as serious adverse events
Notes	Location: 8 sites in Austria, the Czech Republic, and Hungary Cerebrolysin and the randomisation procedure was provided by the manufacturer of Cerebrolysin, Ebewe Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Patients who met all entry criteria were assigned to the treatment groups in a 1:1 ratio, according to a randomisation code generated by a computer software (Ebewe

		Pharma, Unterach, Austria). The randomisation was carried out in blocks of 12 patients, stratified by study centre"
Allocation concealment (selection bias)	Low risk	"For each patient a sealed envelope with information on the actual treatment dispensed was provided to the investigator for emergency cases. All envelopes remained sealed throughout the study"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The investigators and all other study personnel were blind as to the random code assignment until the completion of the statistical analysis". Comment: impossible to assess blinding by outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The investigators and all other study personnel were blind as to the random code assignment until the completion of the statistical analysis". Comment: impossible to assess blinding by outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	25 participants out of 146 randomised were lost to follow-up (17%). Information on the outcomes that are of interest in the review was available only for serious adverse events including death
Selective reporting (reporting bias)	High risk	The trial authors did not report on the time when deaths occurred, and did not assess potential causality with administered medicines "None of the deaths was reportedly related to the study drug administration." With the exception of 1 serious adverse event (hematemesis) in the placebo group, which was rated to be likely related to the study drug, there was no causal relationship to the study drug for any of the serious adverse events, as per the trial authors' assessment
Other bias	High risk	The manufacturer of Cerebrolysin provided the medication and randomisation codes (procedure). No information on funding sources for the trial and no conflict of interest statement was provided

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

Study	Reason for exclusion
Bajenaru 2010	Not a relevant research question; different condition - haemorrhagic stroke; Cerebrolysin given for 10 days only
Bavarsad Shahripour 2011	Reported as an abstract only; Cerebrolysin given for 7 days only (review protocol specifies 14 days)
CASTA 2012	6 publications; Cerebrolysin used for 10 days only (review protocol specifies 14 days at least); efficacy assessment with stroke scales only
CERE-LYSE-1 2012	Cerebrolysin given for 10 days only.
Chen 2013a	Not a relevant condition - mild traumatic brain injury; not relevant outcome - cognitive function
Cuparnecu 2001	Reported as an abstract only; no information on follow-up.
Ershov 2011	No randomisation; Cerebrolysin given for 10 days only; no clinically relevant outcomes measured
Haffner 2001	Reported as an abstract only; efficacy assessment with stroke scales; no information on death
Hong 2002	Cerebrolysin used in rehabilitation after ischaemic stroke.
Hong 2005	Cerebrolysin used for 10 days (review protocol specifies 14 days); efficacy assessment with stroke scales
Jianu 2010	Therapeutic time-window was 72 hours (review protocol specifies 48 hours); randomisation not described
Jin 1999	Cerebrolysin compared with xingnaojing.
Kim 2014	Not a relevant condition - subacute stroke; not relevant outcomes; treatment initiated after 8 days of stroke onset
Makarenko 2006	Reported as an abstract only. Not a relevant research question: Cerebrolysin used to treat infection complications (pneumonia) in people with stroke
Maksimova 2009	Not a relevant research question; different condition - haemorrhagic stroke
Nazarbaghi 2014	Cerebrolysin used for 10 days only (review protocol specifies 14 days); outcome assessed as NIHSS score, not specified by protocol
Ren 2002	Confounded study: disodium cytidine triphosphate or Cerebrolysin used for 10 days
Sagatov 2008	Reported as an abstract only. Not a relevant research question or comparison: Cerebrolysin plus emoxepine versus Cerebrolysin
Shamalov 2005	Reported as abstract only; Cerebrolysin used for 10 days.

(*Continued*)

Shamalov 2010	Not a relevant outcome - the volume of lesion detected by MRI
Shi 1990	Cerebrolysin used in people with cerebral haemorrhage.
Skvortsova 2004	Cerebrolysin used for 10 days only (review protocol specifies at least 14 days)
Skvortsova 2006	No randomisation; Cerebrolysin used for 10 days only.
Skvortsova 2008	Reported as an abstract only. MRI infarct volume as efficacy measure
Stan 2013	Cerebrolysin used for 10 days (review protocol specifies 14 days), wrong outcome - stroke volume
Thong 2009	Reported as an abstract only. Cerebrolysin is not the study drug, used for 10 days only. Wrong comparison
Vilenski 2000	Cerebrolysin used for 5 days.
Vilenski 2006a	Reported as an abstract only. Cerebrolysin compared with Cerebrolysin administered via different routes
Wang 1997	Cerebrolysin in combination with nitrendipine, glucose, and insulin compared with salvia miltiorrihiza in combination with low-molecular-weight dextran. Not a relevant comparison - research question
Wu 1995	Reported as an abstract only. Cerebrolysin used in combination with urokinase
Yavorskaya 2008	Reported as an abstract only. Not a relevant research question: participants with cognitive disorders
Zhang 1994	Non-randomised trial of 27 participants.
Zhang 1997	Not a relevant research question or comparison: Cerebrolysin used in combination with speaking training, mannitol, and conventional therapy versus conventional therapy and mannitol
Zheng 2002	Not a relevant research question or comparison: Cerebrolysin used in combination with citicoline or nicergoline; different efficacy measures - infarction size, neurological function, and motor function
Zhu 2003	Cerebrolysin used in patients with stroke episode duration of 28 ± 7 days; efficacy assessment with stroke scales only

MRI: magnetic resonance imaging
NIHSS: National Institutes of Health Stroke Scale

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

IRCT138803272042N1

Trial name or title	The efficacy of Cerebrolysin in the treatment of acute ischaemic stroke (IRCT138803272042N1)
Methods	Randomised double blind
Participants	100 participants, both male and female, aged 45 to 85 years, the occurrence of acute cerebral ischaemic attack (embolic or thrombotic), hospitalisation during 12 hours of first symptoms of stroke, systolic blood pressure < 200 and diastolic < 100 mmHg Exclusion criteria: recovery of neurologic symptoms after 4 hours of attack, haemorrhagic stroke or the occurrence of stroke in vertebrobasilar system with blood pressure ≥ 200/100 mmHg, seizures, papilledema or rising intracranial pressure (RICP), neck stiffness or symptoms of brain stimulation, the condition of consciousness stupor and coma (Glasgow Coma Score ≤ 6), acute myocardial infarction, National Institutes of Health Stroke Scale < 7 and > 24, hepatic or renal failure, heart failure, dementia, acute infectious disease, doubt the involvement in subsequent brain area (posterior circulation), pregnant women, symptoms of progressive neurological defects, people who are in other trials, people who received piracetam or calcium channel blockers, people who received rt-PA treatment during first 4 hours of symptoms
Interventions	Cerebrolysin (30 mg for first 5 days during the first week and 10 mg for first 5 days in the second, third and fourth weeks) adding to routine therapy
Outcomes	Clinical evaluation of motor ability (speech and motor ability of participants) daily; modified Rankin Scale, National Institutes of Health Stroke Scale; improvement in patients' understanding during the treatment on days 3, 7, 15, and 30; assessment of Clinical Global Impression Scale, Patient Global Satisfaction Score and Mini Mental State Examination by neurologist
Starting date	Recruitment complete. Expected recruitment end date: 23 August 2010
Contact information	Person responsible for scientific inquiries: Dr Majid Gafarpour, Tehran University of Medical Sciences Professor, Neurology Department, Imam Khomeini Hospital, Tohid sq, Tehran, Islamic Republic of Iran Email: ghafarpour@tums.ac.ir
Notes	

DATA AND ANALYSES

Comparison 1. Cerebrolysin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause death	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.29, 2.58]
2 Total number of adverse events	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.69, 3.82]

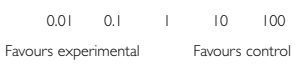
Analysis 1.1. Comparison 1 Cerebrolysin versus placebo, Outcome 1 All-cause death.

Review: Cerebrolysin for acute ischaemic stroke

Comparison: 1 Cerebrolysin versus placebo

Outcome: 1 All-cause death

Study or subgroup	Cerebrolysin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ladurner 2005	6/78	6/68		100.0 %	0.87 [0.29, 2.58]
Total (95% CI)	**78**	**68**		**100.0 %**	**0.87 [0.29, 2.58]**
Total events: 6 (Cerebrolysin), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Not applicable					

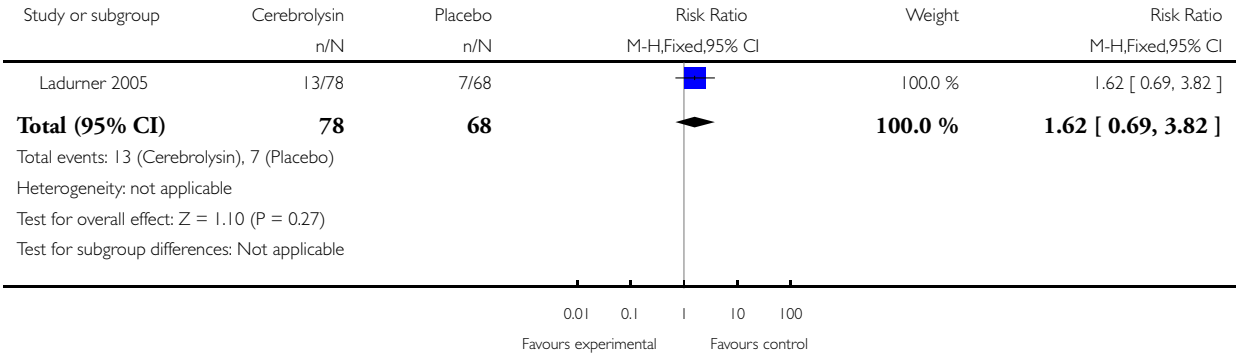


Analysis 1.2. Comparison 1 Cerebrolysin versus placebo, Outcome 2 Total number of adverse events.

Review: Cerebrolysin for acute ischaemic stroke

Comparison: 1 Cerebrolysin versus placebo

Outcome: 2 Total number of adverse events



APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL (the Cochrane Library)
#1 [mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"stroke, lacunar"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"vertebral artery dissection"]
#2 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or anterior next circulation) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab
#3 (isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)):ti,ab
#4 #1 or #2 or #3
#5 (cerebrolysin* or CERE or "FPF-1070" or FPF1070 or "FPF 1070" or "FPF 10-70"):ti,ab
#6 #4 and #5

Appendix 2. MEDLINE search strategy

MEDLINE (Ovid)
1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or stroke, lacunar/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or stroke/ or exp brain infarction/ or vertebral artery dissection/
2. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. 1 or 2 or 3
5. (cerebrolysin$ or CERE or FPF-1070 or FPF1070 or FPF 1070 or FPF 10-70).tw.
6. 4 and 5
7. exp animals/ not humans.sh.
8. 6 not 7

Appendix 3. EMBASE search strategy

EMBASE (Ovid)
1. cerebrovascular disease/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. 1 or 2 or 3
5. cerebrolysin/
6. (cerebrolysin$ or CERE or FPF-1070 or FPF1070 or FPF 1070 or FPF 10-70).tw.
7. 5 or 6
8. 4 and 7
9. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
10. 8 not 9

Appendix 4. WEB of Science Core Collection (including Science Citation Index) search strategy

#1. TOPIC: (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva)
#2. TOPIC: (cerebrolysin*)
#3. #2 AND #1

Appendix 5. LILACS search strategy

cerebrolysin or CERE or FPF-1070 or FPF1070 or cortexin or CORT or N-PEP-12F

Appendix 6. OpenGrey search strategy

cerebrolysin or CERE or FPF-1070 or FPF1070 or cortexin or CORT or N-PEP-12F

Appendix 7. Russian databases search strategy

#1. инсульт or цереброваск * or церебральн * or цвб *

#2. церебролизин or ЦЕРЕ or кортексин or КОРТ
#3. #1 and #2

WHAT'S NEW

Last assessed as up-to-date: 12 April 2015.

Date	Event	Description
27 January 2015	New search has been performed	We performed a new search but did not find any new trials that met the inclusion criteria. There is only one included trial involving 146 participants. We updated the review, including a study flow diagram, a more precise 'Risk of bias' assessment based on GRADE principles, and a 'Summary of findings' table. We refined the conclusions accordingly
27 January 2015	New citation required but conclusions have not changed	We performed a new search. The conclusions have not changed.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 4, 2010

Date	Event	Description
15 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Liliya-Eugenevna Ziganshina (LEZ) prepared the protocol. Tatyana R Abakumova (TRA) performed literature searches of the Russian language studies. LEZ and TRA assessed citations, abstracts, and full texts of trial reports for eligibility; extracted data; and assessed the risk of bias. LEZ drafted the review text.

DECLARATIONS OF INTEREST

LEZ: none known.

TRA: none known.

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Internal sources

- Kazan Federal (Volga Region) University, Russian Federation.

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- Cochrane Stroke Group, UK.
- Liverpool School of Tropical Medicine, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We followed the Cochrane protocol precisely.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Amino Acids [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy]

MeSH check words

Humans