Cerebrolysin for acute ischaemic stroke (Review)

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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 proposed neuroprotective and neurotrophic properties. It is widely used in the treatment of acute ischaemic stroke in Russia and China.

Objectives

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

Search methods

We searched the Cochrane Stroke Group Trials Register (February 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2009), MEDLINE (1966 to February 2009), EMBASE (1974 to February 2009), LILACS (1982 to February 2009), Science Citation Index (1940 to February 2009), SIGLE Archive (1980 to March 2005), and a number of relevant Russian Databases (1988 to February 2009). We also searched reference lists, ongoing trials registers and conference proceedings.

Selection criteria

Randomised controlled trials comparing cerebrolysin with placebo or no treatment in patients with acute ischaemic stroke.

Data collection and analysis

Three review authors independently applied the inclusion criteria, assessed trial quality and extracted the data.

Main results

We included one trial involving 146 participants. There was no difference in death (6/78 in the cerebrolysin group versus 6/68 in the 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

There is not enough evidence to evaluate the effect of cerebrolysin on survival and dependency in people with acute ischaemic stroke. High-quality and large-scale randomised controlled trials may help to gain a better understanding of the potential value of cerebrolysin in acute ischaemic stroke.

PLAIN LANGUAGE SUMMARY

Cerebrolysin for acute ischaemic stroke

Cerebrolysin, a mixture derived from pigs' brain tissue, is widely used in Russia and China. We reviewed evidence from randomised controlled trials investigating cerebrolysin in people with acute ischaemic stroke. This review of one trial, involving 146 participants, showed no clear effect of cerebrolysin for acute ischaemic stroke. No adverse effects specific to cerebrolysin were reported. The medication and methodology of the trial were provided by the manufacturer of cerebrolysin, EBEWE Pharma. There is insufficient evidence that cerebrolysin may be helpful with the management of acute ischaemic stroke.

BACKGROUND

Stroke is the brain equivalent of a heart attack, which occurs when the brain loses its blood and energy supply resulting in damage to brain tissue. Stroke is one of the major causes of disability and mortality all over the world (AHA 2007; Bonita 1990; Bonita 1992). More than 50% of survivors of acute stroke experience severe neurological disorders (loss of vision or speech or both, paralysis and confusion) and these are not restored in 30% to 66% of cases six months after a stroke (French 2006). Annually, 15 million people worldwide suffer a stroke. Of these, five million die and another five million are left permanently disabled, placing a burden on family and community (WHO 2007a).There are 10,000 cases of acute stroke registered in the Russian Federation annually. In 2001, stroke morbidity reached 3.36 per 1000 population with a mortality rate of 40.37% (61.4% for haemorrhagic stroke and 21.8% for ischaemic stroke). The north-west regions had the highest morbidity of 7.43 per 1000, followed by some cities in middle areas (5.37 per 1000) and the far east (4.41 per 1000) (Gusev 2003; Vilenskii 2006).

Pharmacological treatment options

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, such strategies with proven therapeutic effects and an acceptable benefit-to-risk ratio are still lacking. Potential strategies could be grouped according to the existing evidence of their benefits and harms.

Potential benefits

Aspirin appears to be the only treatment that has been shown to be effective when started within 48 hours of onset of ischaemic stroke for early secondary prevention (Sandercock 2008a). Thrombolysis with intravenous recombinant tissue plasminogen activator presents a promising strategy, but only in experienced centres and in highly selected patients (Wardlaw 2009). The evidence has been insufficient so far to identify a preferred thrombolytic agent, the dose, route of administration and the latest time window (Mielke 2004; Wardlaw 2009). Another Cochrane review of trials performed in the pre-controlled trial era suggested a favourable effect of glycerol treatment on short-term survival in ischaemic stroke patients (Righetti 2004). Fibrinogen-depleting agents seem to be promising although more data are needed (Liu 2003).

Potential harms

Tirilazad, an amino steroid inhibitor of lipid peroxidation, increased the combined end-point of 'death or disability' in patients with acute ischaemic stroke (TISC 2001). Lubeluzole, an ion channel modulator of glutamate release that has a benzothiazole structure with proposed 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 has accumulated for the following potential pharmacotherapeutic strategies

Calcium antagonists (Horn 2000); haemodilution (Asplund 2002); excitatory amino acid antagonists, including ion channel modulators and N-methyl-D-aspartic acid (NMDA) antagonists (Muir 2003); anticoagulant therapy, which was not associated with net short or long-term benefits (Gubitz 2004) and did not offer net advantages over antiplatelet agents (Berge 2002); piracetam (Ricci 2006); and a free radical trapping agent NXY-059 (Shuaib 2007).

Evidence from randomised controlled trials is insufficient for conclusions of benefit or harm in the following interventions

Glycoprotein IIb-IIIa inhibitors (Ciccone 2006); ginkgo biloba (Zeng 2005); naftidrofuryl, a 5-HT2 serotonergic antagonist (Leonardi-Bee 2007); low-molecular-weight heparins or heparinoids (Sandercock 2008b); 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 1997); corticosteroids (Qizilbash 2002) and gangliosides (Candelise 2001).

Neuroprotection as a potential strategy

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. Demonstration of benefit in patients with acute ischaemic stroke on clinically relevant outcomes continues to be a challenge. Cerebrolysin is a mixture of low-molecular-weight peptides (80%) and free amino acids (20%) derived from pigs' 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 suggest its potential for treating acute ischaemic neuronal damage. 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 stroke (Makarenko 2005) and spinal cord trauma (Sapronov 2005).

Yet, despite the effectiveness of neuroprotective agents in animal models of stroke, clinical trials of neuroprotective agents in humans have provided disappointing results (Consensus 1998). More recent Cochrane reviews of effects of individual neuroprotective agents and pharmacological groups confirmed this (Gandolfo 2002; Muir 2003; Ricci 2006; TISC 2001). Other means of neuroprotection are being sought. Some neuroprotective agents show beneficial effects on post-hoc analyses, and some studies are still ongoing (Wahlgren 2004). The potential of cerebrolysin for Alzheimer's disease has been systematically reviewed (Fragoso 2002). Cerebrolysin is well accepted by Russian 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 the majority of them carried out in Russia, have accumulated (Chukanova 2005; Gafurov 2004; Gromova 2006; Ladurner 2005; Skvortsova 2004; Wong 2005). There is a need for a systematic evaluation of these results.

The aim of this 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

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

2. To estimate the effect of cerebrolysin on survival and disability.

3. To assess serious adverse events and adverse effects.

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 patients with acute ischaemic stroke. We excluded uncontrolled studies, as well as quasi-randomised controlled trials 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.

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

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

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 searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in February 2009, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1, 2009), MEDLINE (1966 to February 2009) (Appendix 1), EMBASE (1974 to February 2009), LILACS Database (Latin American and Caribbean Health Sciences Literature) (1982 to February 2009), Science Citation Index (1940 to February 2009), SIGLE (System for Information on Grey Literature in Europe) (http://opensigle.inist.fr/) (1980 to March 2005), and the following Russian Databases (1988 to February 2009): Rossiyskaya medicina (http://www.scsml.rssi.ru) and Otkritiy medicinskiy club (http://www.medart.tomsk.ru).

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 2009), National'niy congress cardiologov (2006 to 2009), Rissiyskiy Megdunarodniy Congress Cerebrovascularnaya patologiya i insult (2008 to 2009);
3. searched the following ongoing trials and research registers: the Stroke Trials Registry (http://www.strokecenter.org/trials/), ClinicalTrials.gov (http://clinicaltrials.gov/) and Current Controlled Trials (http://www.controlled-trials.com/).

We attempted to identify all relevant studies regardless of language. We had planned to contact two pharmaceutical companies but this was not done.

Data collection and analysis

Study selection

At least two review authors independently examined all citations and their abstracts and established their relevance and the need to acquire the full article. In cases of uncertainty we obtained the full article. We independently applied the inclusion criteria and resolved disagreements through discussion with all three review authors. All three authors examined the full text of study reports. We only included those studies that met the pre-determined inclusion criteria. We excluded studies that did not meet the inclusion criteria and explained the reason for exclusion in the Characteristics of excluded studies table.

Assessment of methodological quality

All three review authors 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. We made judgments on generation of allocation sequence, allocation concealment, blinding and other risks of bias as adequate (yes), inadequate (no), or unclear, and presented quotes to support our judgments in the Risk of bias table. 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 or with a third party when necessary.

Data extraction

All three review authors independently extracted data using a standardised data extraction form. We extracted data on the methods of studies, participants, interventions, and outcomes. We resolved any differences in the extracted data by referring to the original articles and through discussion or by consulting the third party. We extracted data to allow an intention-to-treat analysis (including all the participants in the groups to which they were originally randomly allocated). 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.

Data analysis

We undertook analysis according to the intention-to-treat principle. We planned to use the Review Manager software to analyse the

data (RevMan 2008). We planned to use relative risk 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. We planned to test for homogeneity of effect sizes between studies using the I^2 test for heterogeneity. If heterogeneity was present ($P < 0.1$), and the number of studies permitted, we planned to investigate it using the following subgroups:

1. dose of cerebrolysin;
2. length of treatment.

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

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. We planned to use funnel plots to examine asymmetry, which may have been caused by publication bias or heterogeneity.

RESULTS

Description of studies

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

The searches identified 23 RCTs for possible inclusion. We excluded 22 of these studies because: (1) the outcomes reported were only either impairment scales or the number of participants with neurological improvement without any of the predefined outcome measures, (2) the study medication was not started within 48 hours of stroke onset and had not been continued for at least 14 days, (3) the research questions were not relevant, (4) the studies used different comparisons, or (5) the studies were reported as abstracts only (Cuparnecu 2001; Haffner 2001; Hong 2002; Hong 2005; Jin 1999; Kulchikov 2008; Kulchikov 2008a; Makarenko 2006; Ren 2002; Sagatov 2008; Shamalov 2006; Shi 1990; Skvortsova 2004; Skvortsova 2008; Vilensky 2000; Vilensky 2006; Wang 1997; Wu 1995; Yavorskaya 2008; Zhang 1994; Zhang 1997; Zhu 2003). We have presented the reasons for exclusion in the Characteristics of excluded studies table.

Only one trial met the inclusion criteria (Ladurner 2005). This was a multicentre placebo-controlled study conducted in Austria, the Czech Republic and Hungary supported by the manufacturer of cerebrolysin, EBEWE Pharma. The trial described the 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. 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 Barthel Index (BI), the Glasgow Coma Scale (GCS), the Clinical Global Impression (CGI), the Mini-Mental State Examination (MMSE), the Syndrome Short Test (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 sixteen were in the control group. We present details of the included trial in the Characteristics of included studies table. There are no trials awaiting assessment and we are not aware of any ongoing trials.

Risk of bias in included studies

Only one RCT met the inclusion criteria. The manufacturer of cerebrolysin, EBEWE Pharma, provided the randomisation method: computer-generated randomisation code. Sealed envelopes allowed for allocation concealment and remained sealed throughout the study. Investigators and all study personnel were blinded. However, it was impossible to assess blinding by outcome. Twenty-five participants out of 146 randomised were lost to follow up (17%). We compared by intention-to-treat 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).

Effects of interventions

The study 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 outcomes 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 risk ratio 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), pneumonia (one in the placebo group). The trialists did not report on the time when those deaths occurred.

Adverse events and effects

The trialists reported the overall incidence of adverse events: 16.4% in the cerebrolysin group and 10.3% in the placebo group. We calculated the risk ratio for the outcome total number of adverse events: RR 1.62, 95% CI 0.69 to 3.82 (Analysis 1.2). The trialists 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 only included trial, supported by the manufacturer of cerebrolysin, EBEWE Pharma, did not provide sufficient evidence of the effects of cerebrolysin on clinically relevant outcome measures for acute ischaemic stroke. 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 and China. The methodological quality of clinical trials of cerebrolysin was not sufficient for inclusion in this review. It is worth mentioning that among the excluded studies, the Skvortsova 2004 trial of cerebrolysin 10 ml and 50 ml versus placebo for 10 days reported no difference in the all-cause death between cerebrolysin and placebo by day 30 after stroke onset. Therefore, the routine use of cerebrolysin in patients 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 of cerebrolysin in acute ischaemic stroke. The potential benefit of neuroprotection for clinical outcomes in acute ischaemic stroke needs to be re-assessed.

AUTHORS' CONCLUSIONS

Implications for practice

The only randomised controlled trial (RCT) that evaluated cerebrolysin for treating acute ischaemic stroke was not designed to enable assessment of clinical outcome measures of efficacy and, thus, does not support the potential clinical benefits of this intervention. The use of cerebrolysin is not supported by reliable evidence. Based on this trial, the routine administration of cerebrolysin to patients with acute ischaemic stroke is not recommended until its effects are tested in larger RCTs.

Implications for research

Future research, if any, needs to focus on well-designed RCTs to assess the potential benefits of cerebrolysin for acute ischaemic stroke. The trialists must ensure that they use pragmatic clinical outcome measures, including as a minimum, early death, dependency, all-cause death and adverse events. The trialists 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 preferably 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 Canadian Neurological Scale 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 (CNS), Barthel Index (BI), Glasgow Coma Scale (GCS), Clinical Global Impression (CGI), Mini-Mental State Examination (MMSE) , Syndrome Short Test (SST), Self Assessment Scale, and the Hamilton Rating Scale for Depression (HAMD) 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	Quote: 'For each patient a sealed envelope with information on the actual treatment dispensed was provided to the investigator

Ladurner 2005 (*Continued*)

		for emergency cases. All envelopes remained sealed throughout the study'
Blinding?	Yes	Quote: '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
Adequate sequence generation?	Yes	Quote: 'Patients who met all entry criteria were assigned to the treatment groups in a 1:1 ratio, according to a randomisation code generated by computer software (EBEWE Pharma, Unterach, Austria). The randomisation was carried out in blocks of 12 patients stratified by study centre'
Incomplete outcome data addressed?	Unclear	Comment: not applicable because the information on the outcomes that are of interest in the review was available only for serious adverse events including death 25 participants out of 146 randomised were lost to follow up (17%)
Free of selective reporting?	Unclear	Comment: not applicable because the information on the outcomes that are of interest in the review was available only for serious adverse events including death
Free of other bias?	No	17% lost to follow up Manufacturer of cerebrolysin provided the medication and randomisation codes (procedure)

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

Study	Reason for exclusion
Cuparnecu 2001	Reported as an abstract only; no information on follow-up
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 (protocol specifies 14 days); efficacy assessment with stroke scales

(*Continued*)

Jin 1999	Cerebrolysin compared with xingnaojing
Kulchikov 2008	Reported as an abstract only Not a relevant research question: viral complications of stroke
Kulchikov 2008a	Reported as an abstract only Not a relevant research question: infection complications of stroke (pneumonia)
Makarenko 2006	Reported as an abstract only Not a relevant research question: cerebrolysin used to treat infection complications (pneumonia) in patients with stroke
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 2006	Reported as abstract only; cerebrolysin used for 10 days
Shi 1990	Cerebrolysin used in patients with cerebral haemorrhage
Skvortsova 2004	Cerebrolysin used for 10 days
Skvortsova 2008	Reported as an abstract only MRI infarct volume as efficacy measure
Vilensky 2000	Cerebrolysin used for 5 days
Vilensky 2006	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
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	Too small (27 patients), probably a non-randomised trial
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
Zhu 2003	Cerebrolysin used in patients with stroke episode duration of 28 $\pm$ 7 days; efficacy assessment with stroke scales

MRI: magnetic resonance imaging

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]

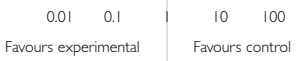
Analysis 1.1. Comparison 1 Cerebrolysin versus placebo, Outcome 1 All-cause death.

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					

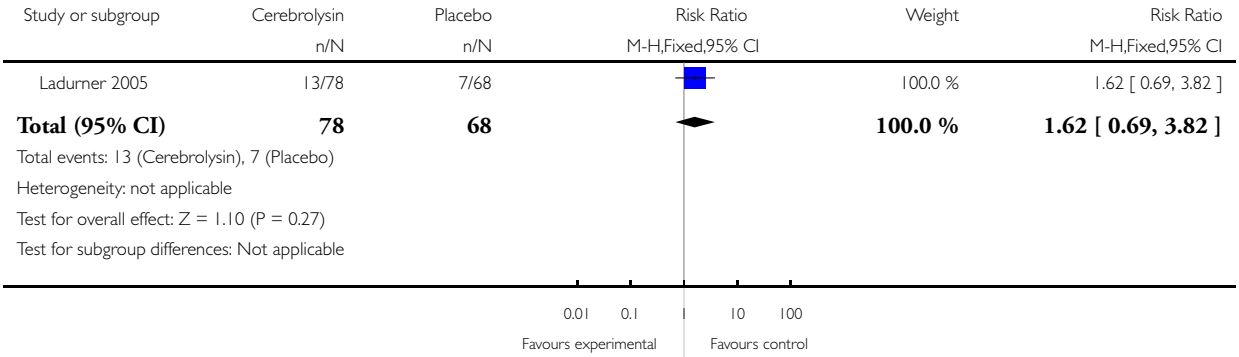


Analysis 1.2. Comparison 1 Cerebrolysin versus placebo, Outcome 2 Total number of adverse events.

Review: Cerebrolysin for acute ischaemic stroke

Comparison: 1 Cerebrolysin versus placebo

Outcome: 2 Total number of adverse events



APPENDICES

Appendix 1. MEDLINE search strategy

We used the following search strategy based on a combination of controlled vocabulary (/) and free text terms (.tw) for MEDLINE (Ovid), and modified it for the other databases.

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or cerebrovascular accident/ or exp brain infarction/ or exp hypoxia-ischemia, brain/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/
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 cortexin$ or CORT or N-PEP-12).tw
6. 4 and 5
7. limit 6 to humans

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

Lilia Ziganshina prepared the protocol. Tatyana Abakumovs and Alexandra Kuchaeva performed literature searches of the Russian language studies. Lilia Ziganshina, Alexandra Kuchaeva and Tatyana Abakumova assessed citations, abstracts and full texts of trial reports for eligibility, and extracted data. Lilia Ziganshina drafted the text of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Kazan State Medical Academy, Russian Federation.
- Cochrane Stroke Group, UK.
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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Amino Acids [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; Stroke [*drug therapy]

MeSH check words

Humans