Neuroprotective treatment with Cerebrolysin in patients with acute stroke: a randomised controlled trial

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Introduction

Cerebrolysin is a compound with neurotrophic and neuroprotective activity. It is produced by enzymatic breakdown of purified brain proteins and consists of low molecular weight peptides and amino acids. Cellular and animal models of cerebral ischaemia have shown that it is a potent neuroprotective agent. We explored the safety and preliminary outcome of Cerebrolysin treatment in patients with acute stroke.

Methods

This was a randomised, placebo-controlled, parallel group trial in which patients with acute stroke were randomised within 24 h of stroke onset to IV therapy with placebo or Cerebrolysin 50 mL/day for 21 days. Both groups received concomitant treatment with ASA 250 mg/day PO and pentoxifylline 300 mg/day IV. Clinical examinations were performed on days 1, 3, 7, 21 and 90 post baseline. Outcome measures were the Canadian Neurological Scale, the Barthel Index, the Clinical Global Impressions, the Mini-Mental State Examination, and the Syndrome Short Test. Treatment emergent adverse events, lab tests, and vital signs were recorded to assess the safety of Cerebrolysin. Since this was an exploratory study no sample size calculations have been performed. Accordingly, statistically significantly better treatment outcomes at day 90 endpoint for Cerebrolysin group were not anticipated.

Results

146 patients were enrolled in two groups: 78 Cerebrolysin and 68 placebo. At baseline, no significant group differences were observed (Table 1). The included group of patients presented with relatively mild neurological symptoms. Patients in the Cerebrolysin group had no significant improvement in the CNS score, the Barthel Index and the Clinical Global Impressions when compared to the placebo group at day 90 observation point. However, in the CNS subscore A1-Motor Functions there was a significant benefit of Cerebrolysin group at days 1, 3, 7, 14 and 21 ($p<0.05$, Fig. 1). No significant treatment differences have been shown with the GCS. The baseline scores for both groups (14.1 for Cerebrolysin and 14.4 for placebo) were very close to the maximum score for GCS (15.0) and thus, no meaningful treatment effects could be detected with this instrument due to a ceiling effect. In the syndrome short test (SST), a significantly better performance of Cerebrolysin patients as compared to placebo was evident ($p<0.05$; t-test). The difference in the MMSE score did not reach statistical significance for the whole group of patients, probably due to higher sensitivity of MMSE to disturbances of speech. However, a highly significant effect of Cerebrolysin versus placebo was observed for the right –sided stroke subgroup ($p<0.001$, Mantel-Haenszel test, Fig. 2). This has been confirmed by significant t-test results in favour of Cerebrolysin for days 1, 3, and 14 after onset of stroke. Both psychometric test scores exhibited a time course similar to the neurological CNS score, with accelerated improvement pattern and greatest improvements during first days after the stroke. Activities of daily living were assessed with the Barthel Index. Cerebrolysin treatment versus placebo did not reach the level of statistical significance due to the overall baseline scores for Barthel indicative of very mild impairment of the patients in this study (Fig. 3), and the resulting ceiling effect of natural recovery. No clinically important effects have been observed in the other outcome measures used in this study except in the Clinical Global Impression where a significant treatment effect of Cerebrolysin was detected in the subgroup of patients treated within 6 hours after the onset of stroke ($p<0.015$; Mantel Haenszel test), again with the time course of improvement consistent with a pattern of accelerated recovery of patients on Cerebrolysin.

Conclusions

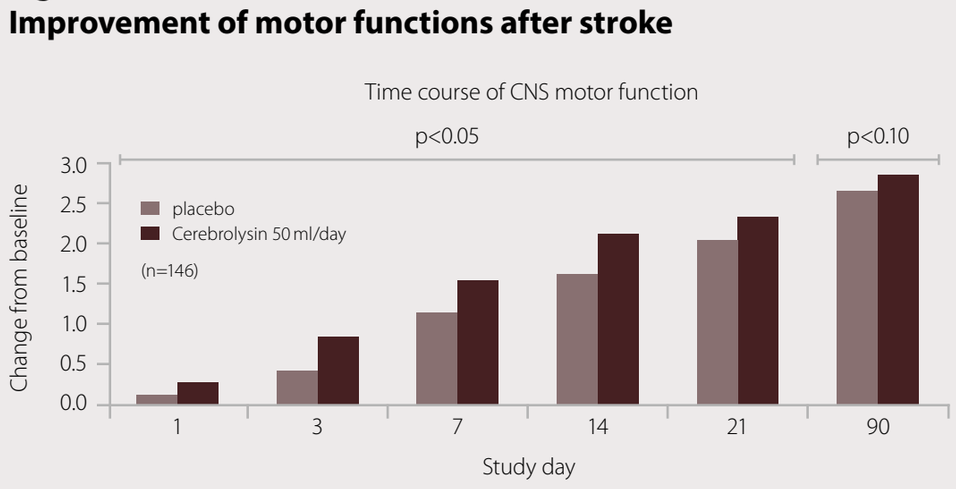
The results demonstrate that neurotrophic treatment with Cerebrolysin is safe and well tolerated by patients with acute stroke. The rather small number of patients in this study, compared to other stroke trials, has impeded the possibility to observe clear-cut treatment effect of Cerebrolysin. Despite the limitations associated with the small sample size and the mild baseline impairment, significant effects of Cerebrolysin on cognitive performance as well as the consistent accelerated recovery pattern were observed as measured with CNS, CGI, BI, SST and MMSE scales. The findings indicate a potential treatment effect of Cerebrolysin in acute stroke. Larger studies, however, are needed to confirm and extend these results.

Table 1.
Selected demographic data and baseline disease characteristics

	Treatment	
	Cerebrolysin (n=78)	**Placebo (n=68)**
Age (years)[1]	65 ± 1.17	65 ± 1.32
Gender (%)		
Male	47 (60.3)	38 (55.9)
Female	31 (39.7)	30 (44.1)
Handedness (%)		
Left	1 (1.3)	0 (0)
Right	77 (98.7)	68 (100)
Side of Stroke		
Left hemisphere	41 (52.6)	31 (45.6)
Right hemisphere	37 (47.5)	37 (54.4)
Duration of Symptoms (h)[1]	12.3 ± 0.73	13.5 ± 1.16
CNS[1]	6.88 ± 0.09	6.68 ± 0.14
GCS[1]	14.1 ± 0.20	14.4 ± 0.16

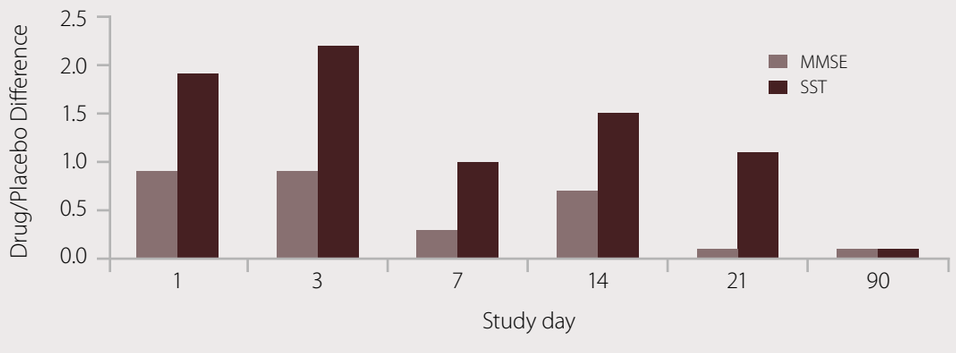
[1] Values are means ± SEM. No significant group differences were observed at baseline

Fig. 1.
Improvement of motor functions after stroke



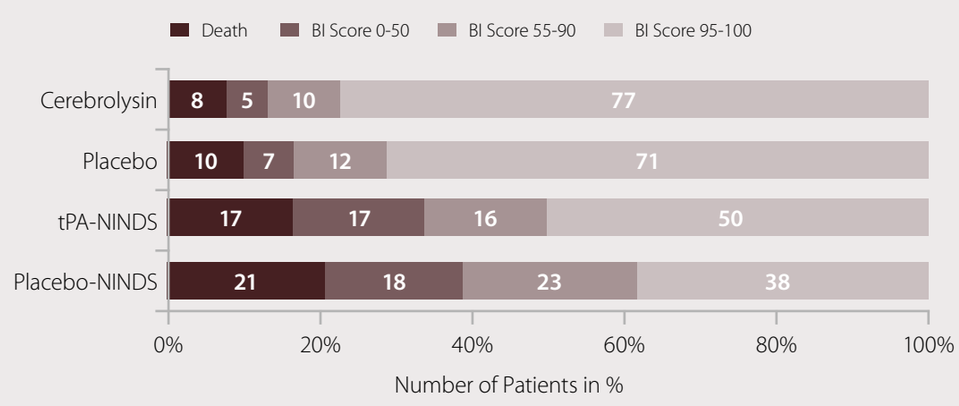
Mean change from baseline in the Canadian Neurological Scale (CNS) for the Cerebrolysin and placebo groups.

Fig. 2.
Outcome and time course of the cognitive scores



Mean score difference between Cerebrolysin and placebo groups in favour of Cerebrolysin-treated patients for the MMSE and SST scores. SST scores showed a significant improvement of Cerebrolysin treated patients versus placebo ($p<0.05$; Mantel-Haenszel test; n=146). MMSE scores also favoured Cerebrolysin treatment but were not significant. Note that the greatest score differences in favour Cerebrolysin were seen in the first days after the onset of the stroke for both scales, indicating an accelerated recovery pattern for Cerebrolysin treated patients.

Fig. 3.
Outcome of the Barthel score at day 90 – comparison to the NINDS r-TPA study



Percentage of patients in each of four categories (death, 0-50 points, 55-90 points, and 95-100 points) of Barthel Index outcome at day 90. The data is compared to the results of the NINDS r-TPA study and indicates that patients in this study on average suffered from milder ischaemic strokes. This is indicated by the lower number of patient deaths and the higher number of patients with full recovery in our study as compared to the NINDS study population. Evidently, a higher percentage of patients on Cerebrolysin achieved a full recovery compared to the placebo group, but this difference did not reach statistical significance.

Table 2.
Patients with serious adverse events. The overall incidence of AEs was similar in both groups

Serious adverse event[1]	**Treatment**	
	Cerebrolysin (n=78)	**Placebo (n=68)**
All SAEs (deaths)	6 (6)	7 (6)
Cerebral infarct (reinfarction)	4 (4)	2 (2)
Heart failure	2 (2)	1 (1)
Pulmonary embolism	0 (0)	2 (2)
Pneumonia	0 (0)	1 (1)
Hematemesis	0 (0)	1 (0)

[1] Adverse events are encoded by Costart Adverse Reaction Terminology

Related References

1. POSTER: W. Lang et al., 2013. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and Cerebrolysin in acute ischaemic hemispheric stroke
2. Original article: J Neural Transm 2005;112:415-428
3. Sample size required for exploratory trials in stroke: D. M. Kerr et al., Seven-day NIHSS is a sensitive outcome measure for exploratory clinical trials in acute stroke: evidence from the Virtual International Stroke Trials Archive. Stroke. 2012 May;43(5):1401-3