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

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Introduction

The neurotrophic drug Cerebrolysin accelerated recovery and prevented acute neuronal damage in preclinical models of ischaemia. Previous clinical trials support therapeutic effects in stroke patients. The study investigated whether the combination with alteplase and Cerebrolysin is safe and can further reduce disability after acute ischaemic stroke.

Methods

This placebo-controlled, double-blind trial involved 119 patients with acute ischaemic hemispheric stroke (Table 1), randomly assigned to a combined treatment with alteplase plus Cerebrolysin or placebo (administered immediately after thrombolytic treatment) starting within three-hours after onset of symptoms. A daily i.v. infusion of 30 ml Cerebrolysin or placebo was given for 10 consecutive days. Primary outcome was the modified Rankin Scale at day 90. A sequential design with interim analyses was applied.

Results

The third interim analysis did not show a benefit in the modified Rankin Scale for Cerebrolysin on day 90 compared to placebo and the study was stopped. The National Institutes of Health Stroke Scale responder analysis (secondary outcome measure, Fig. 1) showed significantly more patients with an improvement of 6 or more points (or a total score of 0 or 1) after two-, five-, 10, and 30 days in the Cerebrolysin group. Similar trends were observed for the modified Rankin Scale responder analysis without achieving statistical significance (Fig. 2 and Table 2). There was no difference between treatment groups regarding adverse events.

Discussion

This trial did not show a statistically significant benefit for the primary outcome on day 90 – defined as disability measured according to the mRS. But the responder analyses for the mRS revealed a positive trend towards accelerated recovery in the Cerebrolysin group at early time points of assessment, in particular at day 5 and 10. This was supported by a statistically significant difference in favour of Cerebrolysin at day 10 for the main mRS analysis (ITT population). Similar results were observed in the responder analyses using the BI and the NIHSS. The biggest difference was achieved at day 10, with a response rate of 72.2% for the Cerebrolysin group compared to 50.8% for the placebo group. The statistically significant difference in favour of the Cerebrolysin group was maintained until day 30, but vanished at the final visit on day 90 for the responder analysis. Cerebrolysin, produced a consistently faster improvement, in all efficacy scales, compared to rt-PA as a stand-alone treatment. The presented trial was powered to detect a difference of 20%, which is quite a large difference for a trial with neuroprotective agents. The current study is the first clinical trial investigating the combination of Cerebrolysin with thrombolytic therapy using rt-PA. To show a 5% difference, which would have been much more realistic for a neuroprotective agent (assuming a 40% control vs. 45% active treatment response rate), with adequate power (80% power % type 1 error two-tailed), 1574 patients per group would have been required.

Conclusions

The combination of Cerebrolysin with recombinant tissue-Plasminogen Activator is safe for treatment of acute ischaemic stroke but did not improve outcome at day 90. During the treatment period with Cerebrolysin (10 days), significantly more patients had a favourable response in neurological outcome measures (National Institutes of Health Stroke Scale) as compared to the placebo group. This transient decrease of neurological impairment has been shown to result in improved cost-effectiveness of thrombolysis in a separate analysis.[3]

Table 1.
Baseline characteristics of patients included in the safety analysis

	Cerebrolysin (n=60)	Placebo (n=59)
Characteristic		
Mean (SD) age (years)	65·5 (11·30)	67·0 (10·56)
Smokers – no. (%)	15 (25·0%)	12 (20·7%)
Males – no. (%)	40 (66·7%)	37 (62·7%)
Mean (SD) time from first symptoms to rt-PA infusion (mins)	142·4 (27·39)	133·4 (34·37)
Mean (SD) NIHSS Score	12·3 (5·39)	11·0 (5·44)
Medical history – no. (%)		
Hypertension	46 (76·7%)	41 (69·5%)
Hyperlypoidemia	20 (33·3%)	16 (27·1%)
Arrhythmia	17 (28·3%)	17 (28·8%)
Coronary heart disease	15 (25·0%)	12 (20·3%)
Obesity	12 (20·0%)	9 (15·3%)
Diabetes of old age	10 (16·7%)	7 (11·9%)
Ealier TIA	6 (10·0%)	6 (10·2%)
Admission to hospital – mean mins (SD)		
Time from First Symptoms to Hospital Admission	82·6 (38·91)	72·5 (30·86)
Time from First Symptoms to rtPA Infusion	142·4 (27·39)	133·4 (34·37)
Time from Hospital Admission to rtPA Infusion	59·9 (36·59)	60·9 (29·04)

Scores on the NIHSS (National Institutes of Health Stroke Scale) range from 0, indicating no neurological deficit, to 42, indicating most severe neurological deficits. TIA denotes transient ischaemic attack. There is no significant difference in any baseline characteristic between the treatment groups.

Table 2.
Responder analysis for primary and secondary end-point in the ITT population*

Outcome variable	Classification	Assessment	*P*-value
mRS score	Responder:	day 5	0·428
	Scores 0 and1	day 10	0·125
	Nonresponder: Scores 2-6	day30	0·366
		day 90	0·984
		LOCF	0·935
NIHSS	Responder:	1 h	0·796
	Improvement of at least 6 points from baseline	2 h	0·259
		day 2	0·024*
	Or total score=0 or 1	day 5	0·002*
	Nonresponder:	day 10	0·019*
	Less than 6 points	day 30	0·038*
	Improvement form	day 90	0·490
	Baseline	LOCF	0·958
	And total score>1		
Barthel Index	Responder:	day 5	0·428
	Score≥95	day 10	0·243
	Nonresponder:	day 30	0·841
	Score<95	day 90	0·673
		LOCF	0·673
Glasgow Outcome Score	Responder:	day 90	0·882
	Score 1		
	Nonresponder:		
	Scores 2-5		

* P-values are those associated to the likelihood ratio chi-square ststistic; LOCF denotes the Last-Observation-Carried-Forward Strategy.

Fig. 1.
Evolution of the National Institutes of Health Stroke Scale (NIHSS) responders for the Cerebrolysin and placebo groups. Defined as improvement of at least 6 points from baseline or total score 0-1. *p<0.05 vs. placebo

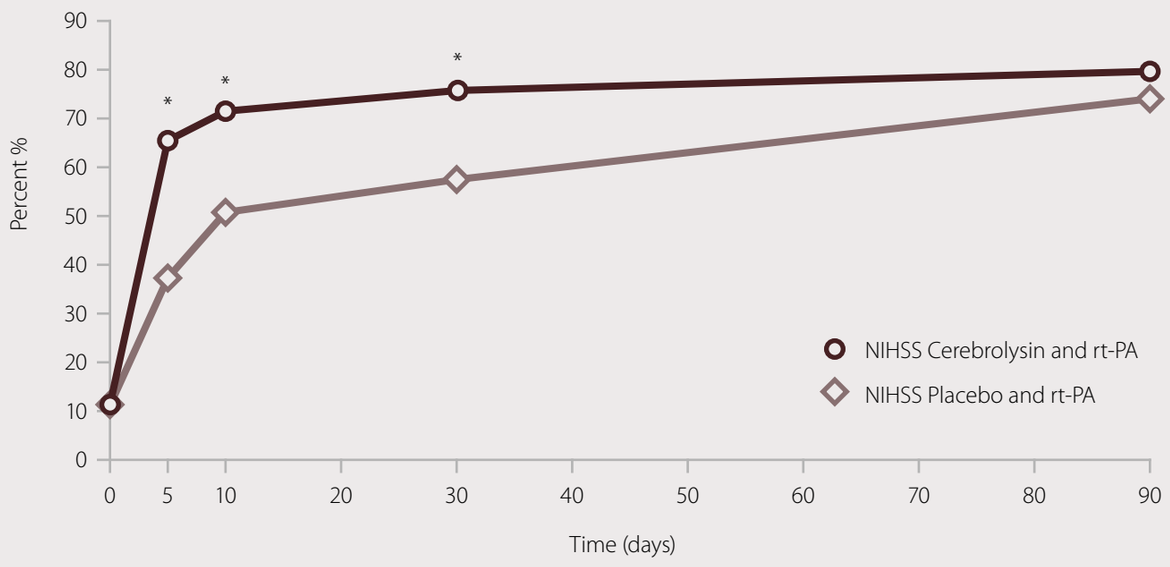
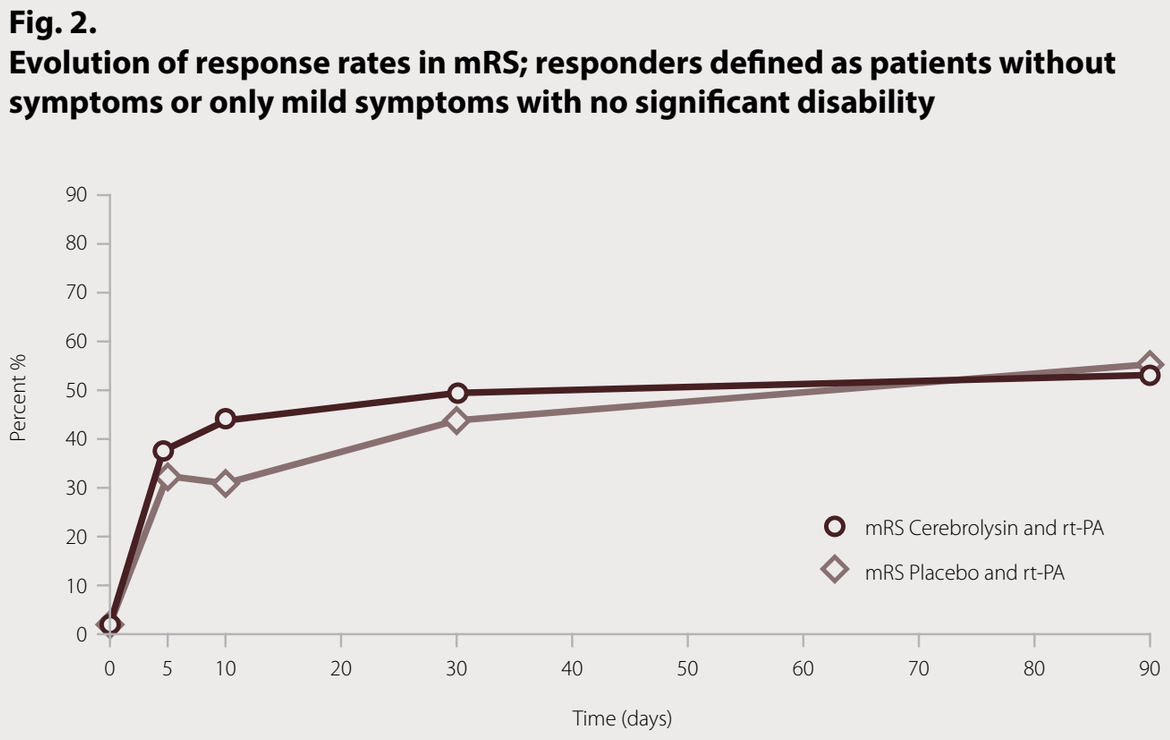


Fig. 2.
Evolution of response rates in mRS; responders defined as patients without symptoms or only mild symptoms with no significant disability



Related references

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