Effects of Cerebrolysin on motor recovery in patients with severe motor impairment after stroke

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Introduction

The aim of this study was to evaluate whether Cerebrolysin provides additional motor recovery on top of rehabilitation therapy in the subacute stroke patients with moderate to severe motor impairment. This phase IV trial was designed as a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. The primary end point of this study was motor function measured by the Fugl-Meyer Assessment (FMA) scores after 3 weeks of treatment. Motor function at 3 months after stroke was also assessed. The plasticity of motor system was assessed by diffusion tensor imaging (DTI) and with resting state functional magnetic resonance imaging (rsfMRI).

Methods

SUBJECTS

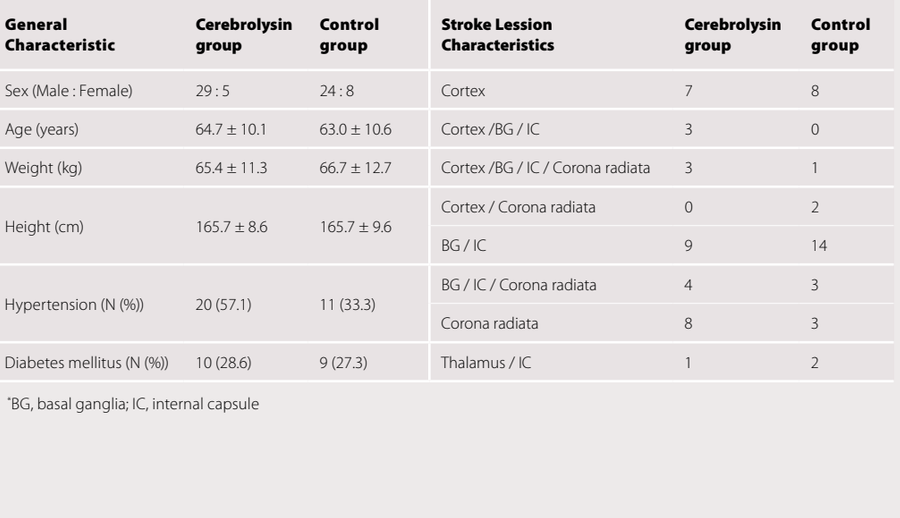
- Inclusion criteria: First-ever cerebral infarction at cortical or subcortical region (unilateral, supra-tentorial), confirmed by CT or MRI in patients recruited at 7 days after stroke onset; with moderate to severe motor function involvement – total of FMA 0-84 and age: between 18 and 80 years; inpatients.
- Seventy subacute stroke patients with hemiparesis were included in this study from four centers in South Korea
- Written informed consent was obtained from all participants prior to inclusion in the study, and the study protocol was approved by the institutional review board

General Characteristic	Cerebrolysin group	Control group	Stroke Lession Characteristics	Cerebrolysin group	Control group
Sex (Male : Female)	29 : 5	24 : 8	Cortex	7	8
Age (years)	64.7 ± 10.1	63.0 ± 10.6	Cortex /BG / IC	3	0
Weight (kg)	65.4 ± 11.3	66.7 ± 12.7	Cortex /BG / IC / Corona radiata	3	1
Height (cm)	165.7 ± 8.6	165.7 ± 9.6	Cortex / Corona radiata	0	2
			BG / IC	9	14
Hypertension (N (%))	20 (57.1)	11 (33.3)	BG / IC / Corona radiata	4	3
			Corona radiata	8	3
Diabetes mellitus (N (%))	10 (28.6)	9 (27.3)	Thalamus / IC	1	2

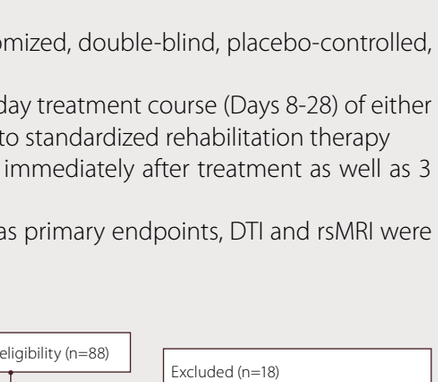
*BG, basal ganglia; IC, internal capsule

EXPERIMENTAL DESIGN

- A phase IV prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group study
- Patients were randomized to receive a 21-day treatment course (Days 8-28) of either Cerebrolysin or placebo, given in addition to standardized rehabilitation therapy
- Assessments were performed at baseline, immediately after treatment as well as 3 months after stroke onset
- Fugl-Meyer assessment scores were used as primary endpoints, DTI and rsMRI were obtained for neuroplasticity assessment



	Days after stroke onset				
	Day 8 (T0)	Day 8-28	Day 29 (T1)	Day 60 (T2)	Day 90 (T3)
Screening	√				
Treatment		√			
Behavioral assessment	√		√	√	√
Neuroimaging assessment	√		√		√
Safety profile	√				√



Test product, dose and mode of administration:

- Group 1: Cerebrolysin – 30 ml dilution/day × 21 days with rehabilitation
- Group 2: Placebo (0.9% NaCl) 100 ml/day × 21 days with rehabilitation

Rehabilitation: 3 hours (NDT: 1 hour, Special PTx: 1 hour, OTx: 1 hour)/day (5 times/week for 3 weeks)

Results

CHANGES OF MOTOR FUNCTION IN ALL PARTICIPANTS WITH A ITT DATA SET

In the ITT analyses set, both groups improved significantly over time in the FMA. However, repeated measures ANOVA showed no significant interaction effect between time and type of intervention as measured by FMA scores (FMA-T, FMA-UL, and FMA-LL). There were no significant differences in the improvement of FMA scores (FMA-T, FMA-UL, and FMA-LL) at T3 between the groups. The improvement of FMA-T and FMA-UL tended to be higher in the Cerebrolysin group than in the control group, but without statistical significance.

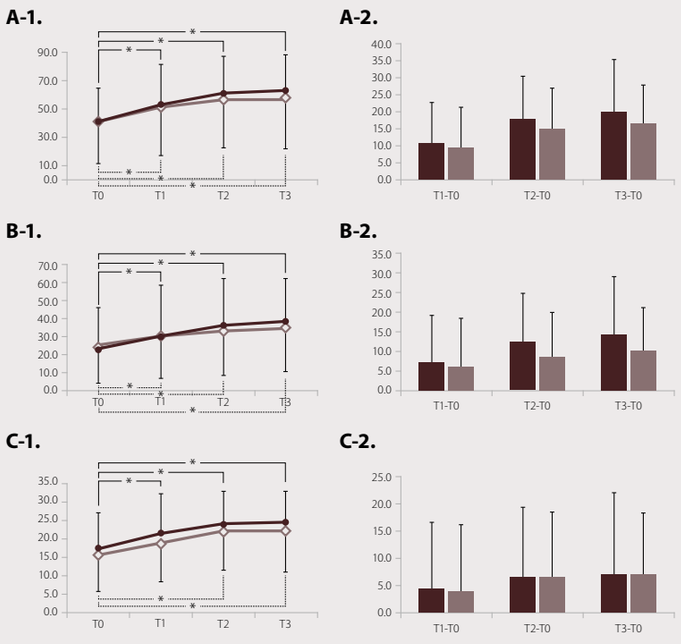


Fig. 1. Changes of FMA in all participants

Measurements were performed at T0 (pre-treatment, 8 days after stroke onset), T1 (immediately after treatment, 29 days after stroke onset), T2 (1st follow-up, 2 months after stroke onset), and T3 (2nd follow-up, 3 months after stroke onset). Error bars represent standard deviation for each group at each time.
A, Total score of Fugl-Meyer assessment. B, Upper limb score of Fugl-Meyer assessment and C, Lower limb score of Fugl-Meyer assessment. 1, Raw score. 2, Improvement ratio

CHANGES OF MOTOR FUNCTION IN PATIENTS WITH SEVERE MOTOR IMPAIRMENT

In the ITT subgroup analysis of patients with severe motor impairment on T0 (n=37; Cerebrolysin n=20, placebo n=17; FMA-T at T0<50), repeated measures ANOVA showed a significant interaction effect between time and type of intervention as measured by FMA-T ($F_{3,102}$=4.596, p<0.05) and FMA-UL ($F_{3,102}$=3.605, p<0.05). In addition, there was a significant group difference in the FMA-T and FMA-UL at T2 and T3.

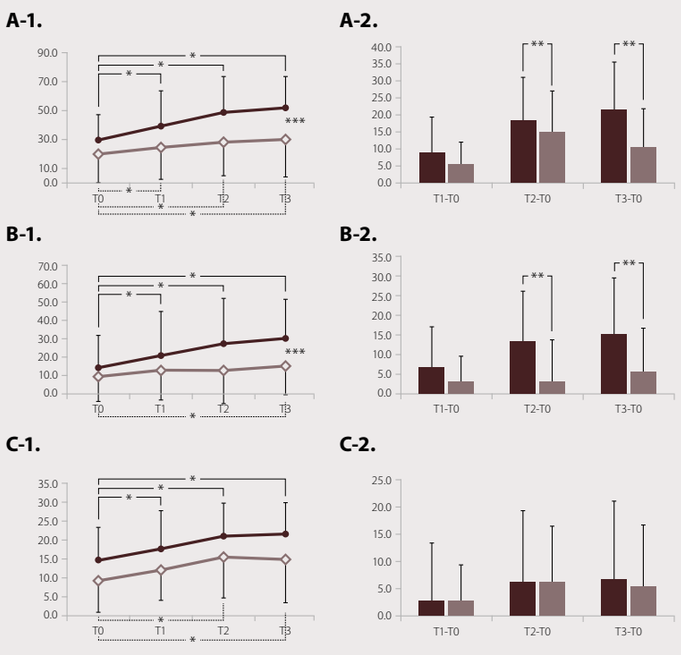


Fig. 2. Changes of FMA in patients with severe motor impairment (FMA<50) at baseline

Measurements were performed at T0 (pre-treatment, 8 days after stroke onset), T1 (immediately after treatment, 29 days after stroke onset), T2 (1st follow-up, 2 months after stroke onset), and T3 (2nd follow-up, 3 months after stroke onset). Error bars represent standard deviation for each group at each time.
A, Total score of Fugl-Meyer assessment. B, Upper limb score of Fugl-Meyer assessment and C, Lower limb score of Fugl-Meyer assessment. 1, Raw score. 2, Improvement ratio

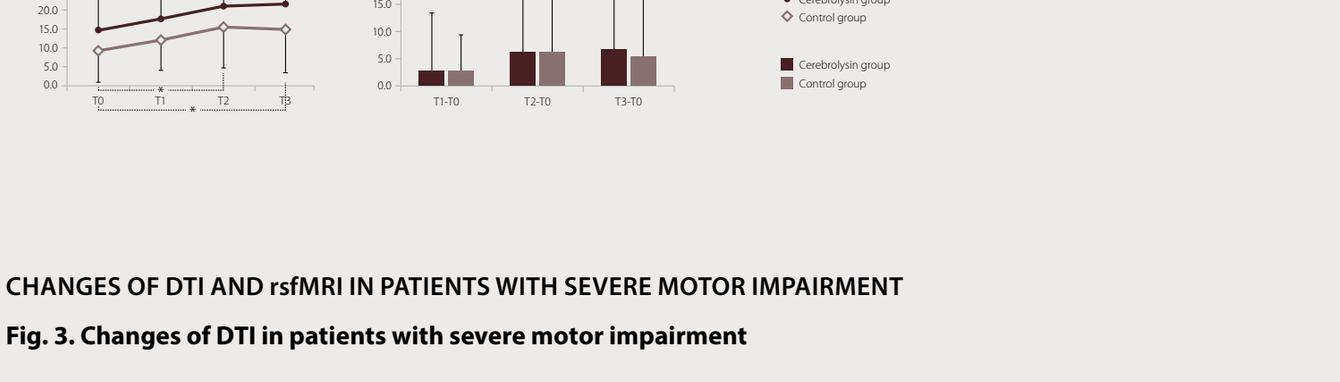
CHANGES OF DTI AND rsfMRI IN PATIENTS WITH SEVERE MOTOR IMPAIRMENT

Fig. 3. Changes of DTI in patients with severe motor impairment

Diffusion tensor imaging (DTI) for Cerebrolysin and placebo at baseline (Day 8, T0), immediately after treatment (Day 29, T1) and three (Day 90, T3) months after stroke onset. A, Fractional anisotropy (FA). B, axial diffusivity (AD). C, radial diffusivity (RD). 1, Time courses. 2, changes from baseline.

Fig. 4. Changes of rsfMRI in patients with severe motor impairment

Resting state of the sensorimotor network as shown by the resting state functional MRI (rsfMRI) for Cerebrolysin (30 ml/day: A1) and placebo (A2) in the affected (AH) and unaffected (UH) hemispheres at baseline (Day 8, T0), immediately after treatment (Day 29, T1) and three (Day 90, T3) months after stroke onset. Time course (B1) and changes from baseline (B2) are given.



Conclusions

The combination of standard rehabilitation therapy with Cerebrolysin treatment in the subacute stroke has shown additional benefit on motor recovery and plastic changes of the corticospinal tract in patients with severe motor impairment.
Cerebrolysin treatment as add-on to a rehabilitation program might be considered as a pharmacologic approach for motor recovery in ischemic stroke patients with severe motor involvement at the subacute stage.

Related references

1. POSTER: Y.-H. Kim et al., 2014. Effects of Cerebrolysin in motor recovery of stroke patients: A diffusion tensor imaging study
2. POSTER: Y.-H. Kim et al., 2014. Effects of Cerebrolysin on motor recovery in patients with subacute stroke

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