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Safety and Efficacy of Cerebrolysin in Infants with Communication Defects due to Severe Perinatal Brain Insult: A Randomized Controlled Clinical Trial

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Background and Purpose The neuroregenerative drug Cerebrolysin has demonstrated efficacy in improving cognition in adults with stroke and Alzheimer's disease. The aim of this study was to determine the efficacy and safety of Cerebrolysin in the treatment of communication defects in infants with severe perinatal brain insult.

Methods A randomized placebo-controlled clinical trial was conducted in which 158 infants (age 6–21 months) with communication defects due to severe perinatal brain insult were enrolled; 120 infants completed the study. The Cerebrolysin group (n=60) received twice-weekly Cerebrolysin injections of 0.1 mL/kg body weight for 5 weeks (total of ten injections). The placebo group (n=60) received the same amount and number of normal saline injections.

Results The baseline Communication and Symbolic-Behavior-Scale-Developmental Profile scores were comparable between the two groups. After 3 months, the placebo group exhibited improvements in the social (p<0.01) and speech composite (p=0.02) scores, with 10% and 1.5% increases from baseline, respectively. The scores of the Cerebrolysin group changed from concern to no concern, with increases of 65.44%, 45.54%, 358.06%, and 96.00% from baseline in the social (p<0.001), speech (p<0.001), symbolic (p<0.001), and total (p<0.001) scores.

Conclusions Cerebrolysin dramatically improved infants' communication especially symbolic behavior which positively affected social interaction. These findings suggest that cerebrolysin may be an effective and feasible way equivalent to stem cell therapy.

Key Words nootropic factor, perinatal brain insult, cerebrolysin, infant, Communication and Symbolic-Behavior-Scale-Developmental Profile, communication defects, symbolic speech development.

INTRODUCTION

Moderate or severe encephalopathy is a major cause of neurodevelopmental disability, and its estimated incidence in the first week of life is 3.75 per 1,000 full-term live births. Only therapeutic hypothermia has proven to be neuroprotective within the first 6 hours postasphyxia.[1-4] The deficits of greatest concern include functional motor and cognitive ones. In one study, more than half of children with cerebral palsy (CP) due to perinatal brain insult had a speech disorder (21%) or could not speak (32%), and speech ability was related to gross motor function, the presence of mental retardation, and the localization of brain maldevelopment.[5] Furthermore, 54% children with CP had more than one associated disability.[6] Researchers have identified a collection of predictors for later language development.

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Emotion and eye gaze, communication, gestures, sounds, words, understanding of words, and object use are language predictors.[7,8] Early identification and management of these language predictors in infants improve later language development.[9,10]

There is as yet no cure or treatment for brain insult in infants and children.

The efficacy, tolerability, and safety of neuroreparative Cerebrolysin therapy has been confirmed in clinical trials involving adults with stroke and Alzheimer's disease.[11,12] Cerebrolysin is a porcine brain-derived preparation of low-molecular-weight neuropeptides (10 kDa) and free amino acids that exhibits pharmacodynamic properties similar to those of naturally occurring neurotrophic factors.[13] Its mechanism of action is thought to be inhibition of apoptosis,[14] and it has also been shown to improve synaptic plasticity and induce neurogenesis in a mouse model of Alzheimer's disease.[15,16] In adults, Cerebrolysin was shown to augment the proliferation, differentiation, and migration of adult subventricular zone (SVZ) neural progenitor cells (i.e., stem cells), contributing to neurogenesis; this finding may in part explain the improvement of neurological outcome with Cerebrolysin therapy after stroke.[17]

The recorded safety and tolerability of Cerebrolysin have led to it being widely used for the treatment of Alzheimer's disease and to prevent disability in adults after cerebrovascular stroke. It is thus possible that this drug has favorable effects in infants, whose brains exhibit a high degree of neural plasticity and reparative capacity in the first 2 years of life. Early intervention after perinatal brain insult may enhance brain plasticity and the recovery of impaired function. In addition, since Cerebrolysin induces stem-cell proliferation in the brain, if it is successful it will be a more cost effective and feasible option than stem-cell transplantation for the treatment of early brain insult.

The aim of this study was to determine the effect of Cerebrolysin on speech development in infants with communication defects caused by severe perinatal brain insult.

METHODS

Participants

This clinical trial study protocol was approved by the review board of the Faculty of Medicine, Ain Shams University, and was conducted in accordance with the ethical principles of the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. The parents or legally acceptable representatives of the infants enrolled in this study provided written informed consent to their participation. This work was part of a study registered with ClinicalTrials.gov (identifier: NCT01059461).

This was an interventional, randomized, placebo-controlled, blinded, safety/efficacy study. One-hundred and fifty-eight infants (78 males and 80 females, aged 6–21 months) with a clinical diagnosis of communication defect due to severe perinatal brain insult were enrolled from the Pediatric Neurology Clinic, Children's Hospital, Faculty of Medicine, Ain Shams University, during the period from March 2011 to September 2013.

Eligibility criteria

All infants were diagnosed with neonatal asphyxia/perinatal brain insult with the criterion of a pH of 7.0 or less or a base deficit of ≥16 mmol/L in a sample of umbilical cord blood or any blood drawn during the first hour after birth. If during this interval a pH of 7.01–7.15, a base deficit of 10–15.9 mmol/L, or a blood gas measurement was not available, the following additional criteria were required: a history of acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest), and either a 10-minute Apgar score of ≤5 or assisted ventilation initiated at birth and continued for at least 10 minutes.[18] Additional enrollment criteria were the presence of concern in one or more composite score components and in the total score of Communication and Symbolic Behavior Scale-Developmental Profile (CSBS-DP). Infants with intractable seizures, or visual and hearing impairments were excluded from the study.

Study design

The CSBS-DP instrument was used to assess prelinguistic communication defects as criteria for enrollment and for assessing the primary outcome after 3 months of study commencement. Interviewers were trained to consistently administer and score in the same manner using the checklist and the cutoffs scoring sheet.

The CSBS-DP is a parent-reported questionnaire that quantifies three subdomains: social and emotional communication, receptive and expressive speech, and symbolic behavior. The instrument's checklist comprises 24 questions that are scored on a scale of 2–4 points within each of the following 7 clusters: emotion and use of eye gaze, use of communication, use of gestures, use of sounds, use of words, understanding of words, and use of objects. The raw score was calculated as follows: 0, 1, and 2 points were given for items checked as "not yet," "sometimes," and "often," respectively. For items that describe a series of numbers or ranges, 0 points was given for items checked "none," and 1–4 points for items containing numbered choices. Cutoffs for the composite and total scores were derived from the CSBS-DP norms based on a perfor-

mance that was 1.25 standard deviations below the mean (the bottom or 10th percentile). These four cutoff scores fall in a range of either "concern" or "no concern" for the three composite scores and the total score.[8]

Patient treatment

Patients who met all inclusion criteria (n=158) were assigned to one of the following two treatment groups at a 1:1 ratio according to a randomization code generated by computer software: Cerebrolysin or placebo. Randomization was conducted in the clinical pharmacy of the pediatric neurology outpatient clinic. The random code assignment meant that the investigators and all study personnel were blinded to the patient group until the statistical analysis was completed. A sealed envelope with information on the given treatment for each infant was provided to the investigators for emergency cases.

Patients assigned to the Cerebrolysin group were given the drug (Ebewe, Arzneimittel, Austria), which is a porcine brain-derived proteolytic peptide fraction, at a dose of 0.1 mL/kg body weight,[19] twice weekly by intramuscular injection for 5 weeks (i.e., ten injections). Those in the placebo group were given saline at 0.1 mg/kg body weight using the same scheduling and route of administration as for the Cerebrolysin group. Concomitant medications (antiepileptic and muscle relaxants) and physiotherapy were continued for all patients, regardless of the group assignment.

Since one of the anticipated side effects of Cerebrolysin was an increased frequency of seizures, electroencephalograms were obtained and, if seizures were detected, they were controlled before enrolling the patients into the study. Safety assessments included monitoring and recording all treatment-emergent adverse events, vital signs, and evaluation for hyperthermia, seizures, and rash.

Primary outcome

The primary outcome of this study was improvement in the CSBS-DP score and change from concern to no concern after 3 months of enrollment in the study.

Statistical analysis

The two groups (Cerebrolysin and placebo) were compared using descriptive statistics and appropriate parametric and nonparametric tests. The paired t-test was used to compare the quantitatively measured parameters, while McNemar's test was used to compare those measured qualitatively. All data analyses were conducted using SPSS (version 18.0, IBM Corporation, Armonk, NY, USA). The threshold for statistical significance was set at $p \leq 0.05$.

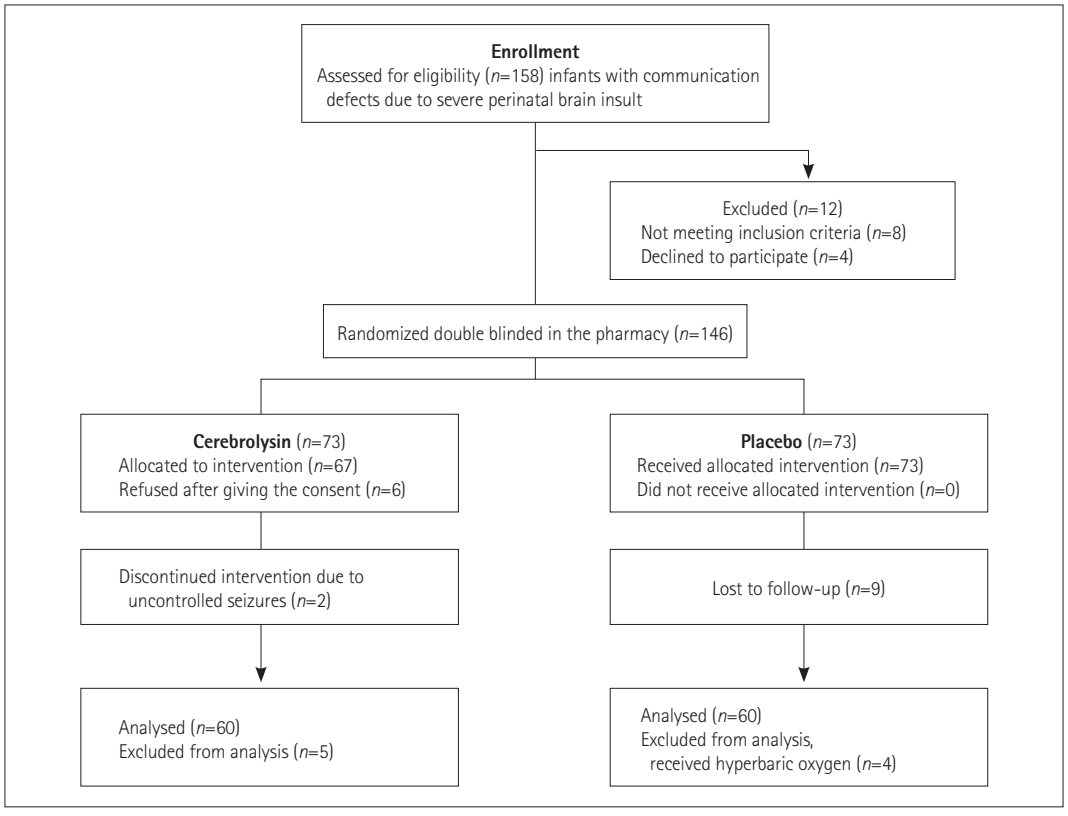

Fig. 1. Flow diagram of the study design.

Table 1. Main baseline demographic and clinical characteristics of the study population

Variable	Placebo group *n*=60	Cerebrolysin group *n*=60	95% CI of the difference		*t*	*p*
			Lower	Upper		
Male sex, *n* (%)	45 (75.0)	36 (59.3)			1.37	0.21
Age, months	13.17 (12.01–14.32)	13.27 (12.07–14.46)	0.06	0.25	1.29	0.20
Social composite score	10 (8.60–11.39)	9.93 (8.53–11.33)	0.07	0.21	0.94	0.35
Symbolic composite score	2.17 (1.7–2.54)	2.07 (1.67–2.46)	0.02	0.22	1.63	0.11
Speech composite score	5.23 (4.51–5.95)	5.23 (4.51–5.95)	0.04	0.07	0.57	0.57
Total score	17.15 (14.80–19.49)	17.10 (14.74–19.45)	0.06	0.16	0.90	0.37

Except where stated otherwise, the data are mean (95% CI) values. 95% CI: 95% confidence interval.

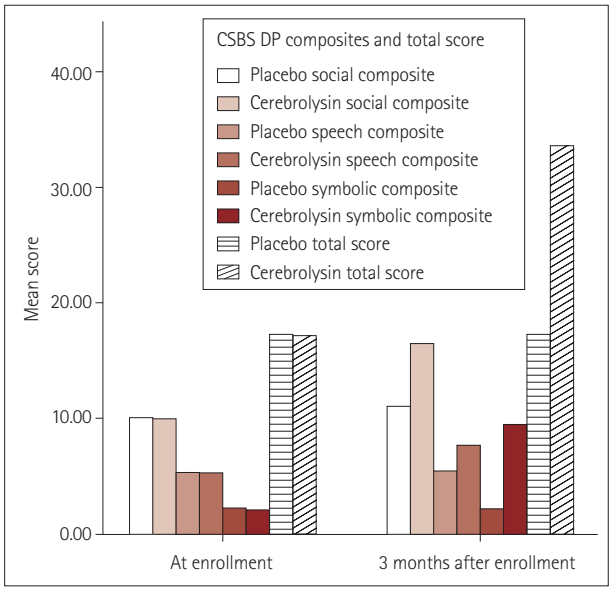

Fig. 2. CSBS-DP scores in the placebo (*n*=60) and Cerebrolysin (*n*=60) groups before and 3 months after enrollment. CSBS-DP: Communication and Symbolic Behavior Scale-Developmental Profile.

RESULTS

Of the 158 infants that were originally enrolled into the study, 146 were randomized to the Cerebrolysin and placebo groups (73 infants in each group). Ultimately, 60 infants in each group completed the study; the data for these 120 infants were included in the statistical analyses. Two patients were withdrawn from the Cerebrolysin group due to intractable seizures (Fig. 1). The age of included infants, which ranged between 6 and 21 months, was comparable between the two groups (p=0.20), as were the baseline CSBS-DP scores: p=0.35, 0.11, 0.56, and 0.37 for the social composite, symbolic composite, speech composite, and p=0.37 total scores, respectively (Table 1).

After 3 months, the placebo group exhibited improved social and speech composite scores (p<0.01 and p=0.024, respectively). No significant improvement was found for either the symbolic composite score (p=0.32) or the total score (p=0.08) (Fig. 2, Table 2).

The Cerebrolysin posttreatment scores (i.e., after 3 months of therapy) were significantly higher than the pretreatment scores for all three CSBS-DP composite scores and the total score. The composite score for the symbolic composite increased dramatically, by more than threefold. The percentage increases from the baseline value (PIBV) for the social composite, speech composite, and symbolic composite scores were 65.44% (p<0.001), 45.54% (p<0.001), and 358.06% (p<0.001), respectively. The PIBV for the total score was 96.0% (p<0.001) (Fig. 2, Table 2). The status of each score before and after Cerebrolysin therapy was compared using a cutoff point (i.e., a qualitative approach). A statistically significant change from concern to no concern after Cerebrolysin therapy was found for all CSBS-DP composites (p<0.001) (Table 3).

Minimal side effects of Cerebrolysin therapy were reported. A mild skin flush occurred in seven children, and irritability that did not interfere with daily life activities on the same day of injection was reported in eight children. There was no change in seizure frequency or in the duration, severity, and antiepileptic drug dose during the study in the Cerebrolysin group, except for two patients who discontinued the study because of intractable seizures that were controlled by discontinuation of Cerebrolysin.

DISCUSSION

The findings of this study demonstrated some improvement in the social and speech composites of the CSBS-DP at follow-up compared to baseline in the placebo group. Notably, at 3 months after Cerebrolysin treatment, the scores were significantly higher than the pretreatment scores for all three CSBS-DP composites and for the total score. The increase was dramatic in the symbolic composite score, with an improvement of more than threefold .

It has been reported that children with CP and intellectual and speech impairments are at risk of limited verbal working memory spans and social functioning.[20,21] In the present study, the improvement in the social composite score with Cerebrolysin supports the value of early intervention in the child's life

Table 2. Comparison of CSBS-DP scores in each group at enrollment and after 3 months of treatment in the placebo (*n*=60) and Cerebrolysin (*n*=60) groups

Variable	Group	Paired differences			*t*	*p**	PIBV
		Mean±SD	95% CI of the difference				
			Lower	Upper			
Social composite score	Placebo	1.03±1.10	0.75	1.32	7.25	<0.01	10.3
	Cerebrolysin	6.50±3.87	5.50	7.50	13.02	<0.001	65.44
Speech composite score	Placebo	0.08±0.27	0.01	0.16	2.32	0.02	1.5
	Cerebrolysin	2.38±2.36	1.77	2.99	7.83	<0.001	45.54
Symbolic composite score	Placebo	0.02±0.13	0.02	0.05	1.00	0.32	0.64
	Cerebrolysin	7.40±1.85	6.92	7.88	30.95	<0.001	358.06
Total score	Placebo	0.05±0.22	0.01	0.11	1.76	0.08	0.29
	Cerebrolysin	16.42±6.04	14.86	17.98	21.04	<0.001	96.00

*Paired *t*-test.
CSBS-DP: Communication and Symbolic Behavior Scale-Developmental Profile, PIBV: percentage increase from the baseline value.

Table 3. Comparison for CSBS-DP score cutoffs in the Cerebrolysin group at enrollment and after 3 months of treatment (*n*=60)

Variable	Status at baseline	Status after 3 months		Total (*n*)	Chi-square	*p**
		Concern, *n* (%)	No concern, *n* (%)			
Social composite score	Concern	6 (11.1)	48 (88.89)	54	46.02	<0.001
	No concern	0 (0.00)	6 (100)	6		
Speech composite score	Concern	0 (0.00)	36 (100)	36	28.66	<0.001
	No concern	2 (8.33)	22 (91.6)	24		
Symbolic composite score	Concern	11 (18.3)	49 (81.6)	60	47.02	<0.001
Total score	Concern	17 (28.3)	43 (71.6)	60	41.02	<0.001

*McNemar's test was used to compare the paired observations.
CSBS-DP: Communication and Symbolic Behavior Scale-Developmental Profile.

and that of his/her family. In addition, no major side effects were observed, except for a tolerable skin flush and irritability on the same day as the injection. The seizure frequency increased in only two patients treated with Cerebrolysin; this epileptogenic side effect was transient and reversible by discontinuation of the drug. Cerebrolysin therapy has been shown to significantly improve cognition, and to be safe and well tolerated in adults and the elderly.[12,22]

The neuroprotectant mechanisms of action of Cerebrolysin are thought to involve neuroimmunotrophic activities, reducing the extent of inflammation, and accelerating neuronal death under pathological conditions such as those observed in neurodegenerative diseases. This may occur through reduction of microglial activation,[23] which leads to augmented proliferation, differentiation, and migration of adult SVZ neural progenitor cells.[17] Furthermore, the intracerebroventricular infusion of Cerebrolysin in rats has been shown to increase the expression of nerve growth factor and its receptor, as well as the expression of the synaptic vesicle protein synapsin. This was found to be associated with specific cellular changes in the hippocampus, including synaptogenesis and cell proliferation.[24]

The timing of initiation of treatment does not appear to affect the outcome. The findings for both acute and delayed Cerebrolysin treatment have revealed a relatively wide therapeutic time window.[25,26] Cerebrolysin was found to improve the cognitive function of patients with mild traumatic brain injury at 3 months after injury, and especially long-term memory and drawing functions.[27] In the present study Cerebrolysin therapy was commenced in the chronic state at the age of 6 months, and not during the acute postasphyxia hypoxic/ischemic brain insult phase. Thus, Cerebrolysin can be effective if started late in the chronic state, and its effects may be long-lasting or even permanent.

Data on the use of Cerebrolysin in pediatric patients are scarce in the literature. Cerebrolysin treatment in girls with Rett syndrome was found to improve behavior, attention level, motor functions, and nonverbal social communication; their EEG parameters were also normalized.[28]

The findings of this study should be considered in light of the small number of enrolled infants. This was due to many parents refusing the use of a drug given intramuscularly, and many of them not continuing to the 3-month follow-up.

The main finding of this study is that only ten injections of Cerebrolysin over a 5-week period dramatically improved communication and language development, and especially symbolic behavior, in these brain-injured infants. This effect will

positively impact family functioning and social interaction. Together with its safety and tolerability, Cerebrolysin gives new hope for the future neuropreventive and curative therapies in infants with severe perinatal brain insult.

Conflicts of Interest

The authors have no financial conflicts of interest.

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