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Assessment of the role of Cerebrolysin in treatment of idiopathic facial nerve paralysis

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Objective
The aim was to evaluate the role of Cerebrolysin in the treatment of Bell’s palsy as a form of peripheral nerve disorder.

Background
Bell’s palsy is a common facial nerve disorder with no available studies assessing the role of Cerebrolysin in its treatment.

Patients and methods
This is a single-blinded randomized clinical trial conducted on 52 patients with Bell’s palsy who were distributed between two groups to receive the classical treatment for Bell’s palsy. Group I received a placebo in the form of normal saline, whereas group II received Cerebrolysin. Both groups were compared regarding the overall rates of recovery and the time intervals between the onset of the disease and the onset of first clinical improvement at one hand and the onset of maximally achieved recovery at the other hand. Moreover, the rate of recovery was correlated with initial electroneurographic value.

Results
Cerebrolysin had no effect on the overall rate of recovery compared with placebo ($P = 0.27$). However, it shortened the time intervals between the onset of the disease and the onset of first clinical improvement at one hand and the onset of maximally achieved recovery at the other hand, with a highly statistically significant difference when compared with placebo ($P < 0.001$ for both). Its effect was more prominent in more severe degrees of nerve degeneration, with no statistical significance ($P = 0.07$).

Conclusions
Cerebrolysin has a therapeutic effect as an adjunctive treatment in the management of idiopathic facial paralysis with a significant effect on the speed of recovery rather than the overall rate of recovery.

Keywords:
bell’s palsy, cerebrolysin, facial nerve, nerve degeneration

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Introduction
Idiopathic facial paralysis also known as Bell’s palsy is one of the most common cranial nerve disorders. It is a lower motor neuron facial nerve paralysis which accounts for $\sim60–75\%$ of cases of acute unilateral facial nerve paralysis. Its incidence is higher among adults, especially pregnant women and diabetics [1].

Several theories have been postulated to explain the etiopathogenesis of Bell’s palsy, with the most common ones being viral infection, autoimmune inflammatory reactions, vascular spasm, and ischemia. All these causes lead to edema of the facial nerve and subsequent compression within its bony canal especially the labyrinthine part [2]. However, there is an agreement about the high recovery rate of this disease over time reaching $80–90\%$ of cases. In addition, conservative treatment represents the main and most effective modality of treatment with systemic corticosteroids gaining a strong and growing evidence. Several studies have suggested a potential role for antiviral drugs in the treatment of Bell’s palsy but have proposed for further evidence [1].

Cerebrolysin is a neurotrophic peptide that stimulates the regeneration of the nervous tissue with protective action. It is used widely for treatment of ischemic and hemorrhagic strokes, traumatic brain injuries, different forms of dementia including Alzheimer’s disease, and cognitive disorders [3]. The aim of this study was to evaluate the role of Cerebrolysin in the treatment of Bell’s palsy as a form of peripheral nerve disorder which can be a therapeutic target for Cerebrolysin.

Patients and methods
This is a single-blinded randomized clinical trial...
conducted on 52 patients with Bell’s palsy recruited from the outpatient clinic of Specialized Medical Care Hospital, Al Ain, United Arab Emirates, during the period from June 2015 to June 2017 after approval of the ethical committee of the hospital. A written consent was taken from every patient before the study.

According to CONSORT criteria, 62 patients were enrolled for the study having unilateral idiopathic facial paralysis (Bell’s palsy) presented during the first week after onset of the disease. A total of 10 patients were excluded owing to having one of the following exclusion criteria: having chronic systemic diseases like diabetes mellitus (five patients), or having a contraindication to the use of Cerebrolysin like hypersensitivity to the drug (three patients), epilepsy (one patient), or experiencing severe renal impairment (one patient).

The remaining 52 patients were allocated to two equal groups by block randomization method using 13 blocks, each comprising four patients, with six patterns for every block, one of which was selected randomly using random numbers generated by Excel program (Microsoft Corp., Redmond, Washington, USA). Group I included 26 patients who received the classic treatment protocol for idiopathic facial nerve paralysis plus a placebo in the form of 5 ml normal saline 0.9%, whereas group II included 26 patients who received the classic treatment protocol plus Cerebrolysin injections. All patients of each group received the planned treatment and completed the follow-up protocol with their data statistically analyzed.

**Baseline assessment**
Every patient included in the study was assessed at the onset of a presentation by history taking to exclude patients with any of the exclusion criteria and to confirm the diagnosis of idiopathic facial paralysis. Clinical examination was performed to assess the House–Brackmann score for staging disability of facial nerve paralysis. In addition, every patient was subjected to electroneurographic assessment of the percentage of facial nerve degeneration. An intradermal skin sensitivity testing was done for every patient to exclude those with hypersensitivity to Cerebrolysin from the study.

**Treatment protocol**
Both groups received the traditional treatment protocol using corticosteroids in the form of prednisone 1 mg/kg orally or 60 mg/day for 5 days, then tapered gradually over 5 days, for a total of 10 days, or prednisolone 25 mg orally twice daily for 5 days, then tapered over 5 days, for a total of 10 days. This was associated with eye care using tear substitutes, lubricants, and eye protection.

Group II received additional treatment in the form of Cerebrolysin 5 ml amp (each ml contains 215.2 mg/ml of Cerebrolysin concentrate in aqueous solution) given intramuscularly every day for 10 days, whereas group I received a placebo in the form of 5 ml normal saline 0.9% given also intramuscularly every day for 10 days. We adopted the least daily dose of Cerebrolysin as specified by the manufacturing company EVER Neuro Pharma (Gmbh, Unterach am Attersee, Austria) to allow for further studies evaluating higher doses.

**Follow-up assessment**
Patients were clinically assessed using the House–Brackmann staging system on a daily basis for 4 weeks followed by a weekly based assessment for a further 4 weeks with a total duration of 8 weeks.

**Outcomes**
Primary outcomes included degree of recovery and the time interval between onset of the disease and onset of the first improvement at one hand and the onset of maximum improvement on the other hand according to House–Brackmann staging system. Secondary outcomes included correlation between the initial percentage of nerve degeneration ‘electroneurographically based’ and degree of recovery in both groups.

**Statistical analysis**
Data were collected, tabulated, and statistically analyzed using statistical package for the social sciences (SPSS) program, version 20, IBM (Armonk, New York, USA). Descriptive statistics for quantitative data were presented as mean and SD. Qualitative data were presented as numbers and percentages. Data turned up to be non-normally distributed according to Kolmogorov–Smirnov test. Mann–Whitney U-test was used to compare quantitative data of both groups. \( \chi^2 \)-Test was used to study the association between two qualitative variables. \( P \) value less than or equal to 0.05 was considered statistically significant.

**Results**
The current study included 52 patients distributed randomly into two equal groups (case and control groups), with 26 patients for each group. There was no significant difference between the two groups regarding age, sex, House–Brackmann stage, and electroneurographic values, reflecting uniformity of both groups (Table 1).

In the current study, there was no significant difference between the two groups regarding the overall degree
of recovery (Table 2). However, there was a highly significant difference between the two groups regarding the onset to first improvement and the onset to maximum improvement intervals in favor for the Cerebrolysin group ($P < 0.0001$ for both) (Table 3).

In the current study, Cerebrolysin helped patients with higher degree of facial nerve degeneration ‘based on the electroneurographic value’ to achieve a better degree of clinical recovery in comparison with the control group but not reaching statistical significance ($P = 0.07$) (Table 4).

### Discussion

Most cases of Bell’s palsy resolve spontaneously. However, treatment aims to minimize the possible complications which include residual facial weakness, synkinesis, autonomic dysfunction like crocodile tears, and facial muscle contracture. As inflammatory edema is the main pathology of Bell’s palsy, corticosteroids with their powerful antiedematous effect remain the main therapeutic agent for Bell’s palsy [1].

Several histopathological studies on patients with Bell’s palsy including autopsies and post decompression biopsies like that of Fisch and Felix [4] confirmed the occurrence of myelin sheath degradation consistent with Wallerian degeneration starting proximal to the geniculate ganglion. Herein comes our rationale for the need of neurotrophic agents to help the regeneration of myelin and to stimulate the functions of Schwann cells.

Cerebrolysin is a neuropeptide preparation that mimics the action of endogenous neurotrophic factors on brain protection and repair. In dementia models, Cerebrolysin decreases β-amyloid deposition and microtubule-associated protein τ- phosphorylation by regulating glycogen synthase-3β and cyclin-dependent kinase 5 activity, increases synaptic density, and restores neuronal cytoarchitecture. These effects protect the integrity of the neuronal circuits and thus result in improved cognitive and behavioral performance. Furthermore, Cerebrolysin enhances neurogenesis in the dentate gyrus, the basis for neuronal replacement therapy in neurodegenerative diseases. Experimental studies in stroke animal models have shown that Cerebrolysin stabilizes the structural integrity of cells by inhibition of calpain and reduces the number of apoptotic cells after ischemic lesion. Cerebrolysin induces restorative processes, decreases infarct volume and edema formation, and promotes functional recovery [5].

The complex composition of Cerebrolysin, the active fraction of which consists of a balanced and stable mixture of biologically active oligopeptides having a total polyfunctional action, does not allow for the usual pharmacokinetic analysis of individual components. Under these conditions, some insight on the pharmacokinetics of Cerebrolysin can only be obtained indirectly. So, it was found that after a single injection, specific neurotrophic activity of plasma may persist for 8 h [5].

Concentrated Cerebrolysin is allowed to be applied in a dosage of 1 ml and up to 10 ml for intramuscular or intravenous injection. Starting with a volume of more than 10 ml and up to 50 ml (maximum dosage), the drug is used for slow drip infusions. Before the procedure, the total volume of the drug is adjusted to 100 ml. For dilution, solutions for infusion (isotonic NaCl solution) are used. The duration of the drip infusion lasts from 15 min to 1 h. The prepared infusion solution should be used immediately as sunlight adversely affects the active ingredients that make up Cerebrolysin, reducing their effectiveness. With a standard scheme of injections of Cerebrolysin, the duration of therapy is 10–20 days of daily intake of the drug. Dose and duration of treatment depend on the nature, severity, and the age of the patient [6].
Tolerability data from studies in patients with dementia indicate that Cerebrolysin was generally well tolerated in all clinical trials. The incidence of any treatment-emergent adverse event was 43.4–64% with Cerebrolysin compared with 38.0–73% with placebo in three larger, placebo-controlled trials in patients with Alzheimer’s disease. Commonly reported adverse events with both Cerebrolysin and placebo included dizziness (or vertigo), headache, increased sweating, nausea, urinary tract infection, depression, and fever, although there was marked variability between studies in terms of the type and incidence of adverse events [6].

Lucas et al. [7] studied the potential effect of Cerebrolysin on peripheral nerve regeneration through the study of its effect on Schwann cell proliferation and function in an in-vitro rat model. They found that Cerebrolysin enhanced the reorganization of Schwann cell clusters and was able to enhance the functions of Schwann cells that are relevant to nerve regeneration. Their findings suggested the potential therapeutic uses for Cerebrolysin to enhance peripheral nerve regeneration.

In the current study, we evaluated the efficacy of Cerebrolysin in the treatment of idiopathic facial paralysis as an adjunctive method of treatment combined with corticosteroids. We found that Cerebrolysin had no effect on the overall rate of recovery compared with placebo. However, it shortened the time intervals between the onset of the disease and the onset of the first clinically recorded improvement on one hand and the timing of maximum recovery on the other hand within 8 weeks of follow-up period, with a statistically significant difference when compared with placebo. Its effect is more prominent in more severe degrees of facial nerve degeneration but not reaching statistical significance.

Up to the author’s best knowledge, there is no available article in the literature evaluating the role of Cerebrolysin in idiopathic facial nerve paralysis. However, there are a number of studies evaluating its role in other peripheral nerve injuries, like optic nerve injury, sciatic nerve injury, or diabetic neuropathy.

Guseva and Dubovskakia [8] evaluated the efficacy of Cerebrolysin used in partial atrophies of the optic nerve, and Cerebrolysin turned out to be highly effective as a drug that improved the outcomes of percutaneous stimulation of the optic nerve. Bogdanov et al. [9] studied patients with clinical features of symmetric diabetic polyneuropathy, and a significant therapeutic effectiveness of Cerebrolysin was revealed for some parameters measured.


Shchudlo et al. [13] analyzed the effect of Cerebrolysin on optic nerves and retinal ganglion cells in a rat model of optic nerve crush. They found that treatment with intraoptic nerve injection of Cerebrolysin was harmful to the optic nerve, whereas its systemic administration had neuroprotective effects on retinal ganglion cells survival and visual function in the optic nerve crush model.

Anosova et al. [15] assessed the dynamics of speech development during the rehabilitation after cochlear implantation for children with sensorineural hearing loss, IV degree, with the use of Cerebrolysin. They found better speech communication strategies and better articulation and cognition with Cerebrolysin.

Dong et al. [16] examined the effects of Cerebrolysin on the treatment of diabetic peripheral neuropathy in a mouse model of type 2 diabetes. They found that the number, diameter, and area of myelinated nerve fibers increased in the sciatic nerves of these mice after intraperitoneal administration of Cerebrolysin.

In conclusion, the findings of our study in the light of the previously mentioned studies revealed the efficacy...
of Cerebrolysin as an adjunctive treatment for Bell’s palsy as a type of peripheral nerve disorder. It has a significant effect on the speed of recovery rather than the overall rate of recovery. This reflects the need for more extended research to evaluate the role of this drug in other peripheral nerve disorders with its potential therapeutic efficacy. In addition, the effect of higher doses and/or longer treatment duration should be evaluated in future studies.

**Conclusion**

Cerebrolysin has a therapeutic effect as an adjunctive treatment in the management of idiopathic facial paralysis with a significant effect on the speed of recovery rather than the overall rate of recovery.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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