The Added Value of Postoperative Neurotrophins/Peptide Mixture in Treating L5 Motor Weakness in Lumbar Disc Prolapse: A Preliminary Report of Multicenter Randomized Controlled Study

Tarek A.A. Abotakia, Wael M.T. Koptan, Ahmad F.A. Allam

Abstract

Background data: Neurotrophins/peptide mixture is a porcine brain-derived peptide preparation with pharmacodynamic properties similar to those of endogenous neurotrophic factors. No study has evaluated the postoperative role of neurotrophins/peptide mixture in the recovery of postdiscectomy motor weakness.

Purpose: This study aims to evaluate the effect of postoperative neurotrophins/peptide mixture treatment on the recovery of L5 motor weakness after lumbar discectomy compared with placebo.

Study design: A prospective randomized controlled study (preliminary report) was conducted.

Patients and methods: In total, 15 patients (group I) with L5 weakness who received a postdiscectomy adjuvant neurotrophins/peptide mixture were compared with group II (15 postdiscectomy patients with L5 weakness) treated with a placebo. The whole patient population was followed up at 2 weeks, 1 month, 3 months, 6 months, and 1 year for assessment of motor recovery.

Results: The mean postoperative Medical Research Council score was significantly improved in both groups; however, the improvement was faster in group I than in group II. The mean Medical Research Council score improvement was significantly higher in group I than that in group II at 2 weeks, 1 month, 3 months, and 6 months; however, it was statistically insignificant at 1 year. At 1-year follow-up, 80% of cases in group I had improved motor power up to grade 5 compared with 40% of cases in group II. The rest of the patients reached grade 4 in both groups. There was no motor deterioration after improvement in either group. There were no reported drug-related adverse effects in group I.

Conclusion: Neurotrophins/peptide mixture may be an efficient and safe adjunctive postoperative treatment for discogenic L5 motor weakness. It may accelerate recovery of nerve injury in an acute setting, which may be a result of accelerating nerve regeneration; however, the overall improvement was comparable to placebo (2022ESJ2601).

Keywords: Cerebrolysin, Lumbar disc, Motor weakness, Neurotrophins, Peptide mixture

Introduction

Intervertebral disc prolapse most commonly occurs between the fourth and fifth lumbar and between the fifth lumbar and first sacral vertebrae; only ~5% become symptomatic [1]. The posterolateral location is the most common direction of herniation (~90–95%) because the lateral extension is the weakest part of the posterior longitudinal ligament, thus causing compression of the traversing L5 nerve root [2]. Progressive and significant motor weakness of dorsiflexion of the big
toe is the most common indication for surgical discectomy [3].

Neurotrophins/peptide mixture (Cerebrolysin) is a mixture of peptides and free amino acids purified from pig brain; it can cross the blood–brain barrier and is believed to have similar effects of endogenous neurotrophic factors on cell growth, proliferation, migration, and differentiation [4,5]. Several fragments of neurotrophic factors have been identified in Cerebrolysin by immunoassay, which is believed to stimulate neurotrophic signaling pathways, including nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, and glial cell line-derived neurotrophic factor [6,7]. Cerebrolysin has been used in several neurological conditions, such as dementia and cerebral stroke, with significant improvement and no reported significant adverse reactions [6,8–10].

No study has evaluated the postoperative role of Cerebrolysin in the recovery of L5 motor weakness. The present study aimed to assess the added effect of Cerebrolysin as a postdiscectomy adjuvant medication for patients with L4–L5 disc prolapse with L5 weakness.

Patients and methods

Between January 2016 and January 2021, 30 patients who presented with L5 motor deficit secondary to lumbar 4–5 disc protrusion/extrusion were included in the study. All included cases had motor power less than grade 4 on the Medical Research Council (MRC) grading scale. The exclusion criteria were as follows: complete L5 motor paralysis (i.e., MRC score 0), spondylolisthesis, translational and angular lumbar instability, diabetes, smoking, epilepsy, renal impairment, and accompanied generalized peripheral neuropathy. Radiological evaluation was accomplished using plain radiograph (anteroposterior lateral and flexion/extension views) and MRI to determine the level of disc herniation, location of the disc (central, posterolateral, and foraminal), percentage of canal compromise, and possible migration of the disc.

Informed consent was given by all participants before surgery after a clear explanation of expected complications and the design of the study. The patients were recruited randomly into two groups, with 15 patients each, by asking them to pick up one of the shuffled sealed envelopes for treatment allocation. All patients were treated by conventional open discectomy under general anesthesia via unilateral fenestration, flavectomy, and removal of the protruded/extruded disc material, and then closure in a standardized fashion.

Postoperatively, group I patients received an adjuvant course of intramuscular Cerebrolysin 5 ml/day, 5 days per week for 4 weeks, whereas group II patients received a placebo in the form of normal saline injection. Both groups had received the same regimen of postoperative NSAIDs in the form of oral celecoxib 200 mg as a single, after-meal dose once daily for 2 weeks. Follow-up was scheduled at 2 weeks, 1 month, 3 months, 6 months, and 1 year postoperatively. Regular neurological examinations and muscle power scoring using the MRC score were performed at each visit, with MRC score improvement calculated. The MRC improvement was formulated mathematically as follows: the deduction of the postoperative score at every follow-up period from the preoperative score. Collected data were analyzed blindly by an independent biostatistician using SPSS software 20 (SPSS Inc., Chicago, Illinois, USA) and MegaStat software version 10.1 (McGraw-Hill). Descriptive statistics was performed for all data; data analysis was done using the χ² test for categorical data and Kruskal–Wallis and Mann–Whitney test for ordinal variables. P values less than 0.05 were considered statistically significant.

Results

No case missed the follow-up schedule in either group. All cases were followed up for at least 1 year. There were three females and 12 males in group I, whereas there were five females and 10 males in group II (P = 0.09). The mean age was 34.3 ± 6.2 (range, 25–49 years) in group I and 31.9 ± 5.6 (range,

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-MRC</th>
<th>2 weeks MRC</th>
<th>1 month MRC</th>
<th>3 months MRC</th>
<th>6 months MRC</th>
<th>12 months MRC</th>
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<td>G I</td>
<td>G II</td>
<td>G I</td>
<td>G II</td>
<td>G I</td>
<td>G II</td>
<td>G I</td>
</tr>
<tr>
<td>Mean</td>
<td>1.73</td>
<td>1.53</td>
<td>3.26</td>
<td>1.66</td>
<td>3.66</td>
<td>1.86</td>
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<tr>
<td>SD</td>
<td>0.59</td>
<td>0.51</td>
<td>0.88</td>
<td>0.48</td>
<td>0.61</td>
<td>0.74</td>
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<td>P value</td>
<td>0.70</td>
<td>&lt;0.0001</td>
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MRC, Medical Research Council.
Mann–Whitney test P value less than 0.05 = significant.
23–44 years) in group II ($P = 0.14$). The mean preoperative MRC scores were found to be of no statistically significant difference between both groups (Table 1). Postoperatively, the mean MRC score was higher in group I in all follow-up periods. These differences were found to be statistically significant in the follow-up periods from 2 weeks to 6 months ($P < 0.001$), whereas they were statistically insignificant at a 1-year follow-up ($P = 0.084$) (Table 1).

In group I, the mean MRC score improved significantly in all follow-up readings ($P < 0.001$). Using post-hoc analysis, the $P$ value was found to be statistically significant at a 2-week follow-up compared with preoperative scores, which became insignificant when compared with the next follow-up readings until 6 months, and then became statistically significant when comparing 6-month values with 1-year values (Table 2). In group II, the mean MRC scores improved insignificantly at 1 month, and then, the $P$ values became statistically significant until the 1-year follow-up (Table 3).

The mean MRC score improvement was higher in group I compared with group II during all follow-up periods. The differences were statistically significant at 2 weeks, 1 month, 3 months, and 6 months. However, at 1-year follow-up, the difference was statistically insignificant (Table 4). At 1-year follow-up, 80% of cases (12 cases) in group I had motor power grade 5, whereas the other three cases reached grade 4. In group II, only 40% of cases (six cases) had motor power grade 5 and the other nine patients reached grade 4 at the final follow-up (Fig. 1). There was no deteriorated case after improvement in either group. There were no reported drug-related complications in group I.

Discussion Cerebrolysin is a complex mixture of balanced and stable biologically active oligopeptides and free amino acids. The neuroprotective properties of Cerebrolysin® are attributed to many constituents as it is believed to contain many nerve growth factors such as glial cell-derived neurotrophic factor [7]. Many theories have been suggested to explain the neuroprotective mechanism of Cerebrolysin, such as reduction of amyloid protein deposition, controlling the expression of interleukin-1 and thus reducing inflammation, reduction of calcium intake in nerve cells, and antagonizing apoptosis by inhibiting the abnormal metabolism of nitric oxide [11–13].

Many clinical studies have been conducted on the beneficial effect of Cerebrolysin in pathological CNS conditions, mostly for brain conditions such as dementia, cerebral stroke, and traumatic brain injuries, with significant improvement, faster recovery, and no reported significant adverse
Table 3. Comparison between the Medical Research Council score in group II at different times.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>2 weeks</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>( P )</th>
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<td>(&lt;0.0001)</td>
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<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2 weeks</td>
<td>1.5 ± 0.51 (1–2)</td>
<td>1.66 ± 0.48 (1–2)</td>
<td>1.86 ± 0.74 (1–3)</td>
<td>2.33 ± 0.81 (1–4)</td>
<td>3.2 ± 0.56 (2–4)</td>
<td>4.4 ± 0.51 (4–5)</td>
<td></td>
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<tr>
<td>1 month</td>
<td>0.9</td>
<td>0.55</td>
<td>0.143</td>
<td>0.37</td>
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<tr>
<td>3 months</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.041</td>
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<td>6 months</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>0.0002</td>
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<tr>
<td>1 year</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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Kruskal–Wallis test post-hoc analysis; \( P \) values for Mann–Whitney test \( P \) value less than 0.05 = significant.

Table 4. Comparison between the Medical Research Council score improvement in groups I and II at different times to pretherapy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>2 weeks MRC improvement</th>
<th>1 month MRC improvement</th>
<th>3 months MRC improvement</th>
<th>6 months MRC improvement</th>
<th>12 months MRC improvement</th>
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<tbody>
<tr>
<td></td>
<td>GI</td>
<td>G II</td>
<td>GI</td>
<td>G II</td>
<td>GI</td>
</tr>
<tr>
<td>Mean</td>
<td>1.5</td>
<td>0.1</td>
<td>1.9</td>
<td>0.3</td>
<td>2.2</td>
</tr>
<tr>
<td>SD</td>
<td>0.92</td>
<td>0.52</td>
<td>0.88</td>
<td>0.9</td>
<td>0.86</td>
</tr>
<tr>
<td>( P ) value</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td>(0.0106)</td>
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</tbody>
</table>

MRC, Medical Research Council.
Mann–Whitney test, \( P \) value less than 0.05 = significant.
reactions [8–10,14]. For spinal cord conditions, there are few experimental studies in the literature, with a conclusion that Cerebrolysin could be a good choice for treating spinal cord injuries [15–17]. Sahib et al. [18], studied the effect of Cerebrolysin on spinal cord injuries in rats and stated that Cerebrolysin enhances spinal cord conduction and reduces blood–spinal cord barrier breakdown, edema formation, and cord pathology after spinal cord injury. In a previous prospective randomized study on 192 patients with cervical spondylotic myelopathy, the authors found that Cerebrolysin was safe and effective in treating cervical spondylotic myelopathy as compared with placebo, without neurologic deterioration over 6 months of follow-up [19]. Sharma et al. [20], conducted a prospective randomized controlled study on 60 operated cases of degenerative cervical myelopathy comparing Cerebrolysin versus placebo for 21 days. More than 66% of patients showed complete neurological recovery in the Cerebrolysin group compared with 56.7% in the placebo; however, this was statistically insignificant. On the contrary, the Cerebrolysin group showed a significant improvement in hand function at 1 year compared with the placebo [20].

Few experimental studies on Cerebrolysin in peripheral neurological lesions are available in the literature. It was found to enhance the reorganization of Schwann cell clusters, which is relevant to nerve regeneration. Lucas, suggested that Cerebrolysin is suitable for therapeutic usage to enhance peripheral nervous system regeneration/reconstruction [20,21]. Haninec et al. [22], tried
intrathecal administration of Cerebrolysin in adult rats after avulsion of the C5 ventral roots and suggested that Cerebrolysin can reduce avulsion-induced loss of adult rat motoneurons. Recently, Haggag et al. [23] evaluated the local application and injection of Cerebrolysin hydrogel after facial nerve axotomy in 72 rats and found a statistically significant improvement in facial nerve regeneration by enhancing Schwann and axonal growth compared with the control group. In another experimental study on peripheral nerve lesions, including posttraumatic brachial plexopathy and compressive radial nerve injury, Cerebrolysin was reported to be associated with more rapid neurological recovery than other therapies, which could support the use of Cerebrolysin in the treatment of acquired peripheral nervous system diseases [24]. Moreover, the effects of intraperitoneal Cerebrolysin injections in type 2 diabetic peripheral neuropathy mouse model revealed that the number, diameter, and area of myelinated nerve fibers increased in the sciatic nerves of these mice after administration of Cerebrolysin [11]. After a thorough review of the literature, the only clinical study performed on the effect of Cerebrolysin on peripheral neurological lesions was a single-blinded randomized clinical trial conducted on 52 patients with Bell’s palsy. The author found that Cerebrolysin did not affect the overall recovery rate compared with a placebo. However, it has a significant effect on the speed of recovery [25].

In this study, we evaluated the efficacy of Cerebrolysin in treating L5 motor weakness as an adjunctive treatment method after surgical discectomy versus surgical discectomy plus placebo. We found that Cerebrolysin, when given after surgical discectomy, had a good effect on the speed of improvement compared with placebo. Although the improvement of MRC was significantly faster in the Cerebrolysin group than that in the placebo group, the overall 1-year MRC and 1-year MRC improvement were statistically comparable between groups; this could be attributed to the small number of populations studied. The small population number of the study is one of its limitations; however, this is a preliminary report and is a part of an ongoing study being carried on a larger scale. More studies with prolonged follow-up periods and a larger population are recommended to assess the therapeutic effect of Cerebrolysin in different peripheral nerve disorders. Moreover, the evaluation of other higher doses and longer duration is recommended in future studies. To the best of our knowledge, this is the first clinical study to evaluate the postoperative role of neurotrophins/peptide mixture Cerebrolysin in compressive motor weakness after decompression.

**Conclusion**

Neurotrophins/peptide mixture (Cerebrolysin) may be an efficient and safe adjunctive postoperative treatment for discogenic L5 motor weakness. It may accelerate recovery of nerve injury in an acute setting, which may be a result of accelerating nerve regeneration; however, the overall improvement was comparable to placebo.

**Conflict of interest**

There are no conflicts of interest.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>PLL</td>
<td>Posterior longitudinal ligament</td>
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<tr>
<td>NTFs</td>
<td>Neurotrophic factors</td>
</tr>
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<td>mJOA</td>
<td>Modified Japanese Orthopedic Association</td>
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<td>VAS</td>
<td>Visual Analogue Scale</td>
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**References**


