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RANDOMIZED TRIAL

Prospective Randomized Control Trial to Compare the Role of Injection Cerebrolysin for 10 Days Duration Against Placebo in Operated Cases of Degenerative Cervical Myelopathy

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Study Design. Prospective randomized control trial.

Objective. To analyze outcomes following the injection of cerebrolysin in surgically treated patients with degenerative cervical myelopathy (DCM).

Summary of Background Data. Previous research has concluded that superior functional outcomes are achieved with the use of cerebrolysin in surgically treated patients of DCM for 21 days. Our study has been conducted to analyze the use of this drug for a shorter duration (10 days) and compare its clinical efficacy.

Methods. Ninety operated cases of mild to severe DCM were randomized into two groups. Sixty patients received the injection Cerebrolysin for 10 days postoperatively. The remaining 30 patients received a placebo. Functional outcomes were measured using modified Japanese Orthopaedic Association (mJOA) scores and visual analogue scale (VAS). The American Spinal Injury Association (ASIA) scale was used to document neurological recovery. Hand function was assessed by measuring the grip strength and the upper limb function score the upper extremity motor mJOA plus upper extremity sensory mJOA score. Assessments were performed and preoperatively and postoperatively and at one-month, three-month, six-month, and one-year following surgery.

Results. Preoperative mJOA and VAS scores were comparable in both groups ($P > 0.05$). Both groups experienced an improvement in mJOA and VAS scores at all time-points during follow-up as compared with preoperative scores. However, the cerebrolysin group demonstrated significantly greater mJOA scores (16.37 ± 1) when compared with the placebo (15.2 ± 1.8) at one-year follow-up ($P < 0.0001$). Neurological improvement with cerebrolysin therapy was also superior ($P = 0.04$). No significant adverse reactions were documented.

Conclusion. Injection cerebrolysin, when administered for 10 days postoperatively, can result in significantly greater neurological improvement and hand function in patients with DCM who also receive surgery.

Key words: cerebrolysin, cervical, degenerative, myelopathy, neuroprotective

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Across the globe, Degenerative Cervical Myelopathy (DCM) is a leading cause of spinal cord dysfunction among adults. Its incidence is expected to rise in the coming decades with changing demographics and an aging population.[1,2] The prevalence of surgically treated DCM is estimated to be 1.6 per 100,000, with most patients diagnosed in their sixth decade, though the true incidence is likely to be higher.[3] Although surgery is often a successful treatment for DCM, many individuals do not recover full function. In an effort to improve functional outcomes following surgical intervention for DCM, some have sought to add cerebrolysin as an adjunct therapy.

Cerebrolysin was derived from porcine brain tissue.[4] It contains enzymatically treated peptides, including brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and ciliary

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TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Clinical and radiologic diagnosis of cervical myelomalacia (C3–C7 levels) with mJOA <15	Traumatic myelopathy
A maximum of 4 levels affected	Myelopathy in congenital stenosis of cervical canal
Age >18 yr	History of cervical spine surgery
Patients managed surgically	Cervical myelopathy due to fluorosis

mJOA indicates modified Japanese orthopaedic association score.

neurotrophic factor. Studies have suggested that it stimulates neural tissues in a mode similar to endogenous neurotrophic factors.

Cerebrolysin has been used therapeutically for acute ischemic stroke. There is limited evidence for its use in traumatic brain injury, schizophrenia, multiple sclerosis, cerebral palsy, and spinal cord injury.[5–7] A recently published pilot randomized control trial suggested that treating patients with cerebrolysin for 21 days after surgical decompression for DCM is associated with superior functional outcomes.[8] However, a 21 days inpatient stay is undesirable, with a great burden placed on patients and families, as well as high associated healthcare costs.

To assess the efficacy of a shorter period of drug administration, this prospective randomized control trial analyses the functional outcomes of patients treated for DCM with cerebrolysin administration limited to 10 days following surgery.

METHODS

This study was conducted at a tertiary care hospital. Institutional review board (IRB) clearance was obtained before commencement. Adult patients were included if undergoing surgery for moderate to severe myelopathy (mJOA <15) (Table 1).

Patients were divided randomly into 2 groups by envelope selection, concealed from the investigator. As prior data already suggested superior results with cerebrolysin administration, of the 90 patients enrolled in the study, 60 were allocated to the cerebrolysin group (group C) and 30 received a placebo for 10 days following surgery (group P).

Decompression was carried out through either an anterior or posterior approach, with or without instrumentation, depending on the clinical presentation and the site of compression. Group C received intravenous cerebrolysin (5 mL diluted in 100 mL 0.9% NaCl over 30 min) once a day for the first 10 postoperative days. Group P received a placebo, administered in a similar manner.

All study-specific data elements were collected preoperatively, immediately after surgery, and then at one month, three months, six months and one year postoperatively by an observer blinded to treatment allocation. Preoperative radiographs, computed tomography, and magnetic resonance imaging were assessed to determine the site of compression and surgical strategy. Functional performance was measured using the mJOA score. Pain was assessed using a visual analogue scale (VAS). Neurological function was assessed using the American Spinal Injury Association (ASIA) impairment scale. Hand function was assessed by measuring grip strength and the upper limb function score. Grip strength was tested using a standard commercially available Digital Palmar Dynamometer. Measurements were taken with the patient seated, shoulder adducted, elbow flexed, forearm neutral, and feet resting on the ground. The test was repeated at 3 intervals, and the scores averaged for each hand—dominant and nondominant. The upper limb function score was calculated as the upper extremity motor mJOA score plus the upper extremity sensory mJOA score and represented a total of eight points. Follow-up radiographs were obtained to evaluate the instrumentation status and alignment of the cervical spine. Postoperative magnetic resonance imaging was only conducted when indicated by new, or persisting, neurological dysfunction.

All data were analyzed using NCSS software, version 12. All data were tested for normality using the Shapiro Wilk test. Sociodemographic and clinical characteristics were assessed at baseline. Both groups were compared for pain, mJOA scores, grip strength, and upper limb function score preoperatively and postoperatively, and at three-month, six-month, and one-year follow-up. The scores were compared across the groups and times using mixed modal Analysis of Variance (ANOVA). Pairwise comparisons were

TABLE 2. Baseline Demographic Data

	Group C	Group P
Age	62.11 ± 6.6	53.23 ± 13.3
Sex	10 females, 50 males	4 females, 26 males
Smokers	11	6
Presence of OPLL	16	9
Mean modified frailty index (11 factor)	2.1	2.2
BMI	21.67 ± 1.65	22.83 ± 1.98

BMI indicates body mass index; OPLL, ossification of posterior longitudinal ligament.

TABLE 3. Results

	Group C	Group P	*P*
OPLL	No, 44 (73.3%) Yes, 16 (26.7%)	No, 21 (70%) Yes, 9 (30%)	0.34
Surgical approach	Anterior, 35 (58.3%) Posterior, 25 (41.7%)	Anterior, 16 (53.3%) Posterior, 14 (46.7%)	0.58
Complications	No, 55 (91.7%) Yes, 5 (8.3%)	No, 27 (90%) Yes, 3 (10%)	0.97
VAS score			
Preoperative (range)	7.38 ± 0.9 (5–9)	7.3 ± 1.2 (4–9)	0.938
Postoperative	5.2 ± 1.2 (3–8)	5.03 ± 1.0 (2–7)	0.081
3 mo	4.05 ± 1.3 (2–8)	3.37 ± 1.0 (1–6)	0.064
6 mo	2.8 ± 1.2 (1–6)	2.73 ± 1.0 (1–5)	0.631
1 yr	1.72 ± 0.8 (1–4)	1.8 ± 0.8 (1–3)	0.089
mJOA Preoperative	12.55 ± 1.8 (9–16)	11.67 ± 1.9 (9–16)	0.732
postoperative	14.17 ± 1.8 (10–17)	13.4 ± 2.0 (10–17)	0.126
3 mo	14.87 ± 1.5 (11–17)	14.33 ± 2.0 (10–17)	0.466
6 mo	15.65 ± 1.5 (11–18)	14.73 ± 1.9 (11–18)	0.089
1 yr	16.37 ± 1 (13–18)	15.2 ± 1.8 (11–18)	< 0.0001

mJOA indicates modified Japanese orthopaedic association scores; OPLL, ossification of posterior longitudinal ligament; VAS, visual analogue scale.

performed using Tukey Kramer Tests. Nonparametric data were analyzed using the Wilcoxon signed rank and Kruskal Wallis test adjusting the *P* value for multiple comparisons with a Bonferroni correction.

RESULTS

Table 2 shows the baseline demographics of each group. No significant differences were observed between the two cohorts. Group C had 50 males, 10 females with an average age of presentation 62.11 ± 6.6 years (range, 42–77 yr). Group P had 28 males, two females with an average age of presentation 53.23 ± 13.3 years (range, 40–75 yr). Ossification of posterior longitudinal ligament was diagnosed in 25 of the patients (16 in group C and 9 in group P). There was no difference in the ASIA grades between the groups.

The mean duration of symptoms before surgery in group C was 6.26 ± 2.45 months (range, 2–24 mo) whereas in group P it was 6.76 ± 2.08 months (range, 0.5–20 mo) ($P = 0.171$). Preoperative mJOA scores and VAS were similar ($P > 0.05$). Anterior decompression was carried out in 50 patients and posterior surgery in 40 patients. Both groups showed statistically significant improvement in mJOA score and VAS score postoperatively at follow-up as compared with their preoperative values ($P < 0.05$; Table 3).

The improvement in mJOA score was significantly greater in group C as compared with group P at one-year follow-up ($P < 0.0001$; Figure 1). Postoperatively, restoration of ASIA grade E was observed in 38 patients in group C as compared with 12 patients in group P ($P = 0.04$; Table 4). VAS scores at one year follow-up did not show any difference between groups (Figure 2). There was no statistical difference at one-year follow-up in mJOA scores when comparing anterior

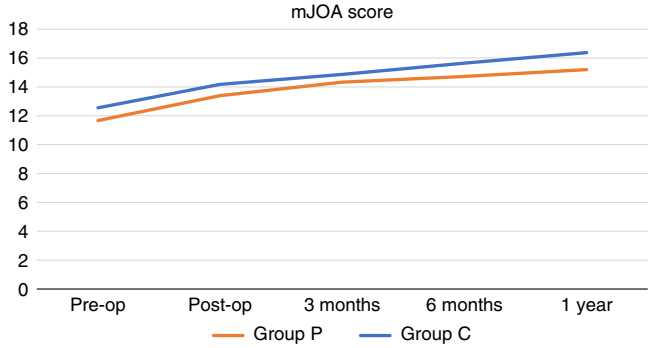

Figure 1. Graph depicting improvement in mJOA scores over a duration of 1 year. mJOA scores were found to be significantly improved in Group C as compared with Group P at one-year follow-up. mJOA indicates modified Japanese Orthopaedic Association. full color online

TABLE 4. ASIA Scores

	Group	ASIA C	ASIA D	ASIA E	*P*
Preoperative	Cerebrolysin	5	35	20	0.57
	Placebo	4	17	9	
Postoperative	Cerebrolysin	1	21	38	0.04
	Placebo	3	15	12	

ASIA indicates American spinal injury association impairment scale.

versus posterior or instrumented *versus* noninstrumented surgeries within the groups.

Hand grip strength (expressed as percentile) improved from 28.5 to 44.6 in the dominant hand for group C and 29.7 to 38.6 for group P. Nondominant hand values improved from 36.4 to 52.8 for group C and 38.6 to 49.6 for group P. Improvements in grip strength postoperatively were found to be significant in both groups (Table 5). The improvement in grip strength for group C was 56.5% and in group P was 30% for the dominant hand. Nondominant hand grip strength improved by 45% for group C and 28.5% for group P.

Preoperative upper limb function scores were comparable in both groups (group C 2.4 ± 1.12 and group P 2.3 ± 0.80; *P* value = 0.556). Scores improved within both groups postoperatively as compared with baseline (Table 6). Group C showed significantly greater improvement in scores at three-month, six-month, and one-year follow-up than group P. At one-year follow-up, scores remained significantly higher for group C 5.8 ± 1.03 as compared with group P 5.1 ± 0.56 (*P* value = 0.011) (Figure 3).

One patient had an episode of headache on day 8 of cerebrolysin therapy and one patient had an episode of dizziness on day 5 of therapy. These symptoms resolved without any medical intervention. No other adverse drug reactions were reported.

DISCUSSION

Our group has previously published an analysis of outcomes after administering cerebrolysin for 21 days following the surgical decompression of DCM, which demonstrated superior neurological and hand function following treatment.[8] However, the various burdens of a 21-day treatment regimen are challenging. Therefore, we sought to test a shorter, more economical regimen, which might improve patient compliance and lower associated healthcare costs. Our results indicate that the administration of cerebrolysin for 10 days following surgical decompression of DCM achieves superior mJOA score, hand function, and neurological function at one year when compared with placebo. No significant adverse reactions were encountered.

Many studies have investigated the mechanism of action of cerebrolysin. Zhang Li *et al.*[9] have shown that cerebrolysin promotes neurogenesis and oligodendrogenesis through stimulating the expression and mRNA modulation of Shh and its receptors. Other work has confirmed the key role of the Shh pathway in post-stroke brain repair and functional recovery and implicated the Shh pathway as a possible target for prolongation of the therapeutic window after stroke.[10] Further research has described cerebrolysin as a neuropeptide preparation that acts similarly to neurotrophic factors.[11] Several fragments of neurotrophic factors have been identified in cerebrolysin by immunoassay, including ciliary neurotrophic factor; glial cell line-derived neurotrophic factor; Insulin-like Growth Factor 1 (IGF1); Insulin-like Growth Factor 2 (IGF2), each of which contribute to the stimulation of neurotrophic signaling pathways. Furthermore, prior work has concluded that cerebrolysin shows brain-derived neurotrophic factor activity by stimulation of the Phosphoinositide 3-kinase/ Protein

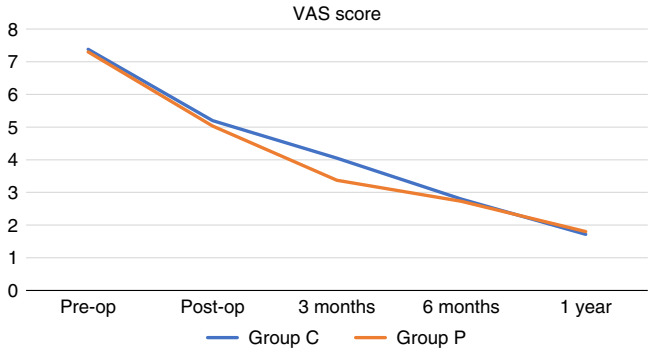

Figure 2. Graph showing improvement in VAS scores over a period of 1-year follow-up. Postoperative VAS scores improved significantly within the group at 1-year follow-up as compared with preoperative scores for both Group C and Group P. VAS indicates visual analogue scale. full color online

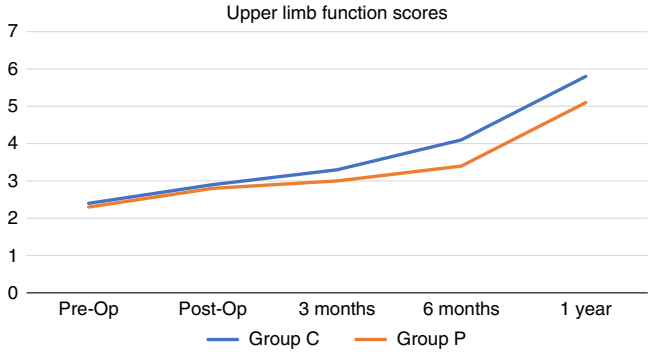

Figure 3. Graph showing improvement in upper limb function scores at one-year follow-up. Scores improved in both groups during postoperative period. Improvement in scores in group C was significantly better. full color online

kinase B or Akt pathway, which plays an important role in cell growth, proliferation, differentiation, and migration.[12]

The AO Spine Research Objectives and Common Data Elements for Degenerative Cervical Myelopathy (AO Spine RECODE-DCM) is an international initiative to create a 'Research Toolkit' in DCM[13]. It has created a list of the top ten unanswered research questions. On this list, priority number eight is the socio-economic impact of DCM. This aims to assess the financial impact of living with DCM on the individual, their caregivers and society as a whole. Davies *et al.*[14] estimated the cost of DCM on society in the United Kingdom. They reported that the annual cost of admission and treatment alone amounted to £38,900,000 whereas the annual cost to society was estimated to be as high as £681,600,000. These estimates were made considering current treatment regimens for DCM. As an adjunct therapy that improves overall function, cerebrolysin has the potential to reduce this burden. A 10-day therapy with cerebrolysin would cost an additional $120; however, the improved clinical outcome after the therapy could enhance productivity, lead to an earlier return to work, reduce the loss of personal income and minimize dependency upon caregivers. Further cost analysis studies are needed to prove this conclusively, but our study supports such consideration in the future.

The major limitation of our study is that it is a single-center experience with a small sample size. Some other limitations, including patient-reported outcomes, were not considered in the results and group-wise comparison based on DCM severity and between 10 days and 21 days of drug administration were not made. Further studies on cerebrolysin in other spine conditions, including dorsal myelopathy and spinal cord injury, will further establish its efficacy as a neuroprotective agent. Oral cerebrolysin is not available in all countries at present. The availability of oral formulations will potentially improve the acceptance of this medication as well as patient compliance and ease of administration. Furthermore, we had a large male preponderance in this study, which we believe may have been influenced by the current social determinants in the country where the study was conducted and gender roles that are still in vogue. There is a greater likelihood of male patients agreeing to enroll in a study due to current social determinants in our environment.

TABLE 5. Grip Strength Measured Using Dynamometer

	Grip Strength, Dominant (Percentile)	Grip Strength, Nondominant (Percentile)
Group C		
Preoperative	28.5	36.4
Postoperative 1 yr	44.6	52.8
Change	16.1	16.4
% change	56.5	45
P value	0.0007	0.001
Group P		
Preoperative	29.7	38.6
Postoperative 1 yr	38.6	49.6
Change	8.9	11
% change	30	28.5
P	0.004	0.002

TABLE 6. Upper Limb Function Scores

Upper Limb Function Scores	Group C	Group P	*P*
Preoperative	2.4 ± 1.12	2.3 ± 0.80	0.556
Postoperative	2.9 ± 0.40	2.8 ± 0.25	0.744
3 mo	3.3 ± 1.86	3.0 ± 1.90	0.028
6 mo	4.1 ± 3.14	3.4 ± 2.50	0.043
12 mo	5.8 ± 1.03	5.1 ± 0.56	0.011

Upper limb function scores is upper extremity motor mJOA score + upper extremity sensory mJOA score.

CONCLUSION

Injection cerebrolysin, when administered for 10 days postoperatively, can result in significantly greater neurological improvement and hand function in patients with DCM who also receive surgery.

➢ Key Points

- ❑ Cerebrolysin has been widely studied for its neurotrophic, neuroprotective, and neuro-regenerative properties.
- ❑ Only one study has been published recently for the use of Cerebrolysin for 21 days duration in operated cases of DCM, which showed improved neurological recovery and hand function.
- ❑ Present study considers the use of Cerebrolysin for 10 days in operated cases of DCM- thus, decreasing the duration of therapy, reducing cost, and better compliance of the patient.
- ❑ Our study concludes that the use of Cerebrolysin in operated cases of DCM for 10 days is safe, has significant improvement in neurology, and improves hand function.
- ❑ This improved clinical outcome after the therapy would mean better productivity, early return to work, a decrease in loss of personal income, and lesser dependency upon caretakers.

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