A retrospective, multi-center cohort study evaluating the severity-related effects of Cerebrolysin treatment on clinical outcomes in traumatic brain injury

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CNS & Neurological Disorders – Drug Targets, 2015, 14, 000-000

Introduction

The severity-related effects of Cerebrolysin, a neurotrophic compound, on TBI clinical outcome have not been investigated. Thus, and taken into account experimental and clinical experience with the drug, we postulated that the administration of Cerebrolysin as adjunctive therapy would be well tolerated and would foster short-term recovery independently of TBI severity. In order to test our hypothesis, in the present study we examined whether adding Cerebrolysin to the standard medical care of patients with mild, moderate and severe head injuries improved functional recovery and clinical outcome. We also documented the safety profile of Cerebrolysin in these patients.

Methods

A total of 7,769 adult patients with TBI who were admitted to 10 Romanian neurosurgery departments between 2005-2010 were included in this retrospective study. All of the patients were managed according to standard guidelines on medical-surgical care of TBI. Additionally, some (1,618) patients received Cerebrolysin® (EVER Neuro Pharma, Austria) as an adjuvant therapy beginning within the first 48 hours after TBI. The clinical outcomes were ranked according to the Glasgow Outcome Scale (GOS) and the Modified Rankin Disability Score (RDS) at 10 and 30 days post-TBI. Analyses of efficacy were performed separately for subgroups with mild, moderate or severe TBI according to Glasgow Coma Scale (GCS) scores at admission. The following factors were used as inclusion criteria: age over 18 years, mild to severe closed head injury according to the Glasgow Coma Scale (GCS), admission within 48 hours of TBI onset, discharged or follow-up at 10 days and follow-up at 30 days. The exclusion criteria included the following conditions: life-threatening multiple trauma, other associated severe conditions, epilepsy, concomitant stroke, pregnancy, lactation, concomitant medication with neuroprotective or nootropic effects, vasoactive drugs or psychotropic drugs. Efficacy and safety evaluations were done by personnel not involved in any treatment decision concerning the evaluated patients. The Cerebrolysin-treated patients were grouped into 2 different drug regimens (20 ml/day or 30 ml/day, administered through i.v. infusion), each of which was compared with the control group. Of the patients on Cerebrolysin treatment, 1,142 received 20 ml/day, and 476 were treated with the 30 ml/day dose. The duration of the Cerebrolysin treatment varied from 1 to 30 days, and the median treatment duration was 10 days.

Results

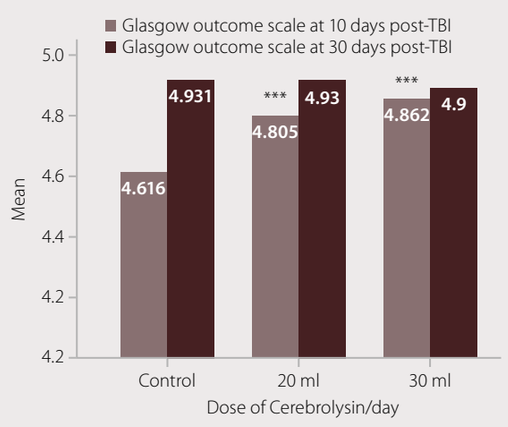
Brain damage severity, as determined via the GCS score at admission, is presented in Table 1. The average GCS score at admission was significantly lower ($p<0.001$) in the Cerebrolysin group (10.9 ± 3.8) than in the control group (13.2 ± 3.3). Within the Cerebrolysin group, 745 patients (46.0%) were classified as having mild TBI, 406 patients (25.1%) were classified as having moderate TBI, and 467 patients (28.9%) were classified as having severe TBI; whereas 4,787 (77.8%), 604 (9.8%) and 760 (12.4%) patients had mild, moderate or severe TBI, respectively, in the control group. This distribution reflects a more marked clinical severity ($p<0.001$) in Cerebrolysin-treated patients than in control group cases. Surgical treatment was performed in 437 patients (27.0%) in the Cerebrolysin group compared with 1,526 patients (24.8%) in the control group (no significant difference). The proportion of patients with moderate or severe TBI was higher in the Cerebrolysin group than in the control group; thus, analyses of efficacy were performed separately for the subgroups of mild, moderate and severe TBI patients.

Table. 1. Severity of trauma in study population

	Control	Cerebrolysin	Significance
GCS score	**N (%)**	**N (%)**	
3	132 (2.1)	47 (2.9)	
4	177 (2.9)	97 (6.0)	
5	63 (1.0)	60 (3.7)	
6	154 (2.5)	79 (4.9)	
7	123 (2.0)	96 (5.9)	
8	111 (1.8)	88 (5.4)	
9	101 (1.6)	56 (3.5)	
10	137 (2.2)	98 (6.1)	
11	107 (1.7)	88 (5.4)	
12	259 (4.2)	164 (10.1)	
13	250 (4.1)	157 (9.7)	
14	789 (12.8)	259 (16.0)	
15	3,748 (60.9)	329 (20.3)	
Average GCS score	**mean±SD**	**mean±SD**	**Significance (t-test)**
	13.20±3.26	10.94±3.76	F: 200.57; df:7767; p<0.001
GCS-related severity:	**N (%)**	**N (%)**	**Significance (Chi-Square)**
3-8 (severe)	760 (12.4)	467 (28.9)	X^2: 632.57; df:2; p<0.001
9-12 (moderate)	604 (9.8)	406 (25.1)	
13-15 (mild)	4,787 (77.8)	745 (46.0)	
Total number of cases	6,151 (100)	1,618 (100)	

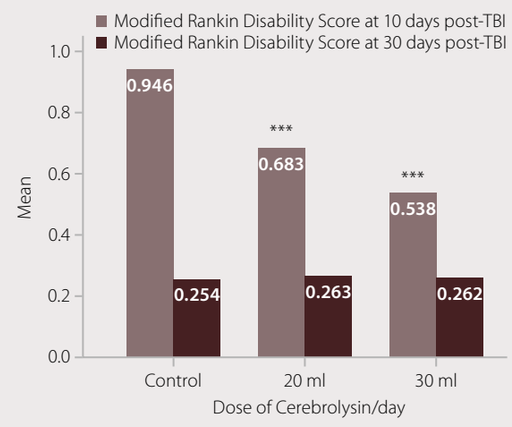
GCS: Glasgow Coma Scale. Differences between groups for the distribution of the indicated parameters (GCS score; GCS-related severity) were analyzed by using the chi-square test. The percentages refer to each particular group of patients.

Fig. 1. GOS scores at 10 and 30 days post-TBI in the treatment groups of mild TBI patients



The control group is designated as Cerebrolysin 0 ml/day. At 10 days post-TBI, the average GOS score was significantly higher in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group. ***p<0.001 for the Bonferroni post-hoc test at 10 days compared with the controls.

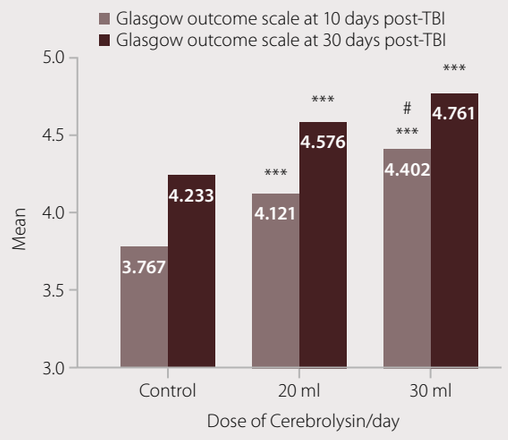
Fig. 2. RDS scores at 10 and 30 days post-TBI in the treatment groups of mild TBI patients



The control group is designated as Cerebrolysin 0 ml/day. At 10 days post-TBI, the average RDS score was significantly lower in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group. ***p<0.001 for the Bonferroni post-hoc test at 10 days compared with the controls.

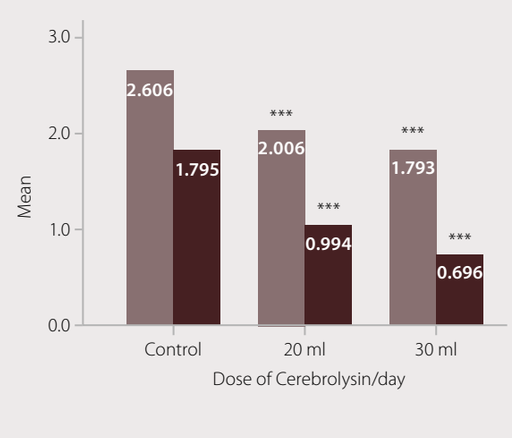
Fig. 3. GOS scores at 10 and 30 days post-TBI in the treatment groups of moderate TBI cases

The control group is designated as Cerebrolysin 0 ml/day. At 10 and 30 days post-TBI, the average GOS score was significantly higher in both 20 ml and 30 ml Cerebrolysin treatment groups compared to the control group.



At 10 days, the average GOS score was significantly higher in the 30 ml Cerebrolysin treatment group compared with the 20 ml Cerebrolysin treatment group. ***p<0.001 for the Bonferroni post-hoc test at 10 and 30 days compared with the controls; #p<0.05 for Cerebrolysin 30 ml/day compared with Cerebrolysin 20 ml/day at 10 days.

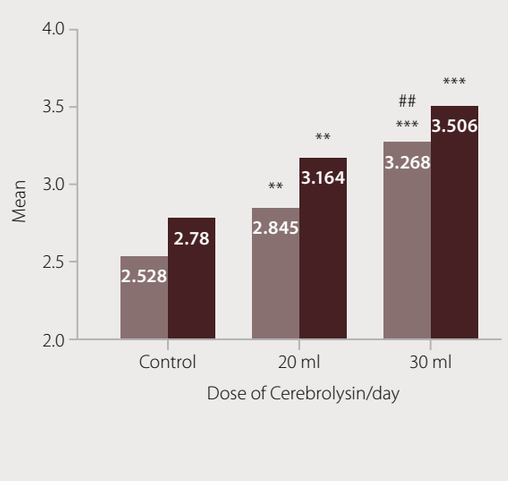
Fig. 4. RDS scores at 10 and 30 days post-TBI in the treatment groups of moderate TBI cases



The control group is designated as Cerebrolysin 0 ml/day. At 10 and 30 days post-TBI, the average RDS score was significantly lower in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group. ***p<0.001 for the Bonferroni post-hoc test at 10 and 30 days compared with the controls.

Fig. 5. GOS scores at 10 and 30 days post-TBI in the treatment groups of severe TBI patients

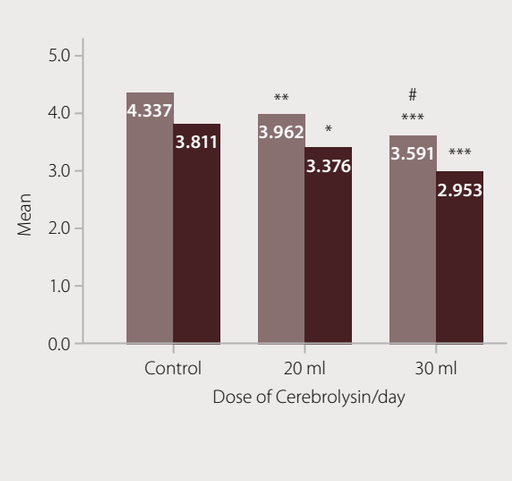
The control group is designated as Cerebrolysin 0 ml/day. At 10 and 30 days post-TBI, the average GOS score was significantly higher in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group.



At 10 days, the average GOS score was significantly higher in the 30 ml Cerebrolysin treatment group compared with the 20 ml Cerebrolysin treatment group. **p<0.01 and ***p<0.001 for the Bonferroni post-hoc test at 10 and 30 days compared with the controls; ##p < 0.01 for Cerebrolysin 30 ml/day compared with Cerebrolysin 20 ml/day at 10 days.

Fig. 6. RDS scores at 10 and 30 days post-TBI in the treatment groups of severe TIBI patients

The control group is designated as Cerebrolysin 0 ml/day. At 10 and 30 days post-TBI, the average RDS score was significantly lower in both the 20 ml and 30 ml Cerebrolysin treatment groups compared with the control group.



At 10 days, the average RDS score was significantly lower in the 30 ml Cerebrolysin treatment group compared with the 20 ml Cerebrolysin treatment group. *p<0.05, **p<0.01 and ***p<0.001 for the Bonferroni posthoc test at 10 and 30 days compared with the controls; #p<0.05 for Cerebrolysin 30 ml/day compared with Cerebrolysin 20 ml/day at 10 days.

Table. 2. Adverse events reported more frequently in each treatment group

Adverse Event	Control N (%)	Cerebrolysin-20 N (%)	Cerebrolysin-30 N (%)	Significance (Chi-Square)
Nausea	291 (4.73)	37 (3.23)	21 (4.41)	X^2: 5.00; df:2; ns
Diarrhea	46 (0.74)	18 (1.57)	8 (1.68)	X^2: 10.34; df:2; p<0.01
Constipation	682 (11.08)	105 (9.19)	41 (8.61)	X^2: 5.85; df:2; ns
Urinary tract infection	249 (4.04)	61 (5.34)	15 (3.15)	X^2: 5.37; df:2; ns
Allergic reaction	21 (0.34)	3 (0.26)	1 (0.21)	X^2: 0.38; df:2; ns
Hypertension	348 (5.65)	72 (6.30)	19 (3.99)	X^2: 3.63; df:2; ns
Pyrexia	521 (8.47)	94 (8.23)	45 (9.45)	X^2: 0.67; df:2; ns
Insomnia	301 (4.89)	65 (5.69)	28 (5.88)	X^2: 1.97; df:2; ns

Differences between groups for the distribution of the indicated parameters were analyzed by using the chi-square test. The percentages refer to each particular group of patients.

Conclusions

According to the results of this large retrospective study, Cerebrolysin seems to be effective in improving clinical outcome and functional recovery after traumatic brain injury. Cerebrolysin, acting as a neurotrophic multimodal agent with pleiotropic neuroprotective effects, may interfere with the pathogenic mechanisms of TBI at multiple levels to promote neuroprotection and neurorestoration. The extrapolation of these positive results, however, is limited by the lack of randomization and control of such a retrospective study. Further prospective controlled clinical trials are needed to confirm the clinical efficacy of Cerebrolysin in TBI patients suggested by our results.

Related references

1. Original article: CNS & Neurological Disorders – Drug Targets, 2015, 14, 000-000

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