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ORIGINAL ARTICLE

Efficacy and safety of cerebrolysin in neurorecovery after moderate-severe traumatic brain injury: results from the CAPTAIN II trial

Dafin F Muresanu[1,2] · Stefan Florian[1] · Volker Hömberg[3] · Christian Matula[4] · Nicole von Steinbüchel[5] · Pieter E Vos[6] · Klaus von Wild[7] · Codruta Birle[1,2] · Ioana Muresanu[1,2] · Dana Slavoaca[1,2] · Olivia Verisezan Rosu[1,2] · Stefan Strilciuc[1,2] · Johannes Vester[8]

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Abstract

Introduction The objective of this trial was to evaluate the efficacy and safety of Cerebrolysin in treating patients after moderate to severe traumatic brain injury (TBI) as an adjunct to standard care protocols. The trial was designed to investigate the clinical effects of Cerebrolysin in the acute (neuroprotective) stage and during early and long-term recovery as part of a neurorestorative strategy.

Materials and methods The study was a phase IIIb/IV single-center, prospective, randomized, double-blind, placebo-controlled clinical trial. Eligible patients with a Glasgow Coma Score (GCS) between 7 and 12 received study medication (50 ml of Cerebrolysin or physiological saline solution per day for 10 days, followed by two additional treatment cycles with 10 ml per day for 10 days) in addition to standard care. We tested ensembles of efficacy criteria for 90, 30, and 10 days after TBI with a priori ordered hypotheses using a multivariate, directional test, to reflect the global status of patients after TBI.

Results The study enrolled 142 patients, of which 139 underwent formal analysis (mean age = 47.4, mean admission GCS = 10.4, and mean Baseline Prognostic Risk Score = 2.6). The primary endpoint, a multidimensional ensemble of 13 outcome scales, indicated a "small-to-medium"–sized effect in favor of Cerebrolysin, statistically significant at day 90 ($MW_{combined} = 0.59$, 95% CI 0.52 to 0.66, $P = 0.0119$). Safety and tolerability observations were comparable between treatment groups.

Conclusion Our trial confirms previous beneficial effects of the multimodal, biological agent Cerebrolysin for overall outcome after moderate to severe TBI, as measured by a multidimensional approach. Study findings must be appraised and aggregated in conjunction with existing literature, as to improve the overall level of insight regarding therapeutic options for TBI patients. The widely used pharmacologic intervention may benefit from a large-scale observational study to map its use and to establish comparative effectiveness in real-world clinical settings.

Keywords Traumatic brain injury · Cerebrolysin · Multidimensional approach · Wei-Lachin pooling

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✉ Dafin F Muresanu
dafinm@ssnn.ro

[1] Department of Neurosciences, "Iuliu Hatieganu", University of Medicine and Pharmacy, No. 43 Victor Babes Street, 400012 Cluj-Napoca, Romania

[2] RoNeuro Institute for Neurological Research and Diagnostic, Cluj-Napoca, Romania

[3] Department of Neurology, SRH Gesundheitszentrum Bad Wimpfen GmbH, Bei der alten Saline 2, 74206 Bad Wimpfen, Germany

[4] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria

[5] Institute of Medical Psychology and Medical Sociology, University Medical Centre Göttingen, Göttingen, Germany

[6] Department of Neurology, Slingeland Hospital, Kruisbergseweg 25, 7009 BL Doetinchem, Netherlands

[7] Medical Faculty, Westphalia Wilhelm's University, Münster, Germany

[8] Department of Biometry and Clinical Research, idv Data Analysis and Study Planning, Gauting, Germany

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Introduction

Traumatic brain injury (TBI) is a colossal public health problem with an estimated lifetime economic cost of over $76.5 billion in the United States (USA) alone, according to the Centers for Disease Control and Prevention (CDC). The pathophysiology of TBI consists of a complex cascade of primary and secondary occurring vascular, inflammatory and metabolic processes resulting in astroglial and neuronal damage [1].

Despite an increase in overall incidence, TBI-related hospital admissions have seen declining trends, mostly attributable to prevention efforts spearheaded by the World Health Organization and the development of comprehensive treatment and management guidelines. The high prevalence of significant residual morbidity in individuals who sustained a head trauma [2–4] has prompted researchers to test a myriad of pharmacologic interventions for TBI with very little success in the last decades. According to an in-depth review performed in 2010, the majority of randomized controlled trials (RCTs) used a single outcome measure model with arbitrary dichotomization of continuous variables and had other essential flaws, notably not adjusting the research design to the complexity of TBI [4].

In 2013, the IMPACT study group reported recommendations for future research that aim to improve the statistical power of future Randomized Controlled Trials with up to 50% by addressing baseline heterogeneity and adding sensitivity to the efficacy analyses by using a multidisciplinary, multidimensional approach [5]. Continually changing patterns and mechanisms of injury due to the aging global population have pushed scientific inquiry to understand the underlying processes that lead to secondary damage [6] and to identify interventions that may promote neurorecovery in TBI [7, 8]. A drug with potential beneficial effects on recovery from TBI is Cerebrolysin, a combination of peptides (active fragments of neurotrophic factors) and amino acids obtained from highly purified lipid-free brain proteins, which promotes neuroprotection and neurorecovery: neurotrophic stimulation (survival and maintaining the phenotype of highly differentiated cells), neuromodulation (changes in neuronal and synaptic plasticity), and metabolic regulation (against lactic acidosis and increase in resilience against hypoxic conditions) [9]. Cerebrolysin has been associated with improved Glasgow Outcome Scale and modified Rankin Scale scores in a recent meta-analysis of four cohort studies [10]. The biological agent has also registered enhanced cognitive performance in a sample of mild TBI patients [11].

The CAPTAIN II trial used a multidimensional approach to evaluate the efficacy and safety of Cerebrolysin for the treatment of patients after moderate to severe TBI as an additional component to standard care.

Materials and methods

CAPTAIN II, a single-center, prospective, randomized, double-blind, placebo-controlled clinical trial, was approved by the Ethics Committee of the University of Medicine and Pharmacy in Cluj-Napoca, Romania (No. 714/07.03.2013). A full study protocol is available in the ISRCTN registry (No. 17097163). The study enrolled patients with moderate to severe traumatic brain injury who were eligible to receive the drug according to the inclusion and exclusion criteria (Table 1) within 4 h of injury. The trial lasted for 90 days after injury. One group received pharmacological treatment with Cerebrolysin, and the second group received a saline solution.

The primary objective of the study was to assess the effects of Cerebrolysin on general and neurocognitive outcomes after traumatic brain injury. Three ensembles of efficacy criteria for 90, 30, and 10 days after TBI were tested according to the principle of a priori ordered hypotheses by a multivariate, directional test approach, reflecting the global status of patients after TBI. The study also documented adverse events and mortality of any cause.

Study procedures

Assessments were performed at the following visits: (1) screening and baseline, (2) day 10, (3) day 30, and (4) day 90. The control group was administered 250 ml 0.9% NaCl intravenously in three treatment courses (days 1–10, 31–40, 61–70). The treatment group received Cerebrolysin diluted in 0.9% NaCl to a total volume of 250 ml intravenously (50 ml for days 1–10 and 10 ml for days 31–40, 61–70).

Treatments were assigned according to a predefined randomization plan. A study-specific randomization code was prepared using the program Research Randomizer within a validated working environment at the Emergency County Hospital (Cluj-Napoca, Romania). Randomization was undertaken in a 4:3 ratio of Cerebrolysin to placebo. In accordance with the ICH Biostatistics Guideline, the block size was intentionally not provided in the study protocol. At randomization, patients were assigned the lowest patient number available. The allocated treatment group applied for all three treatment cycles. If a patient did not progress to the 2nd or 3rd cycle, treatment packs initially allocated to this patient were destroyed. Patients, healthcare providers, data collectors, and outcome assessors were blinded to treatment allocation. All treatment packs were identical in appearance, and the study medication label of the ready-to-use infusion solution was the same for all treatment groups. Since Cerebrolysin is an amber-colored solution, colored infusion lines, syringes, and infusion bags were used for drug administration.

Table 1 Inclusion and exclusion criteria used for patient enrolment in the CAPTAIN II trial

Inclusion criteria
Clinical diagnosis of TBI and a GCS score of 7–12 at the time of hospital admission. Pre-hospital intubation/sedation/paralysis was accepted if the GCS score had been assessed before intubation/sedation/paralysis by trained staff.
Isolated TBI (abbreviated injury score (AIS) in other body regions of ≤ 2).
CT (Marshal classification) I to VI (from diffuse injury to the non-evacuated mass lesion).
Pre-Trauma Karnofsky Index = 100. If no corresponding information was available before the start of treatment (e.g., the patient was unconscious or not able to communicate) and no information was retrieved within 24 h after the start of treatment, the patient remained in the study. If no information was available before the start of treatment and a violation of the Karnofsky Index was detected within 24 h after the start of treatment, the patient was withdrawn from the study, and the treatment medication was stopped.
Age between 18 and 80 years.
Ability to provide written informed consent for enrollment.
Reasonable expectancy of patient's ability to comply with the protocol requirements for the duration of the study, in the investigator's judgment.
Time to needle for study medication within 4 h from injury.
Exclusion criteria
Patients with polytrauma (AIS score in other body regions of > 2).
Patients with spinal cord injury.
History of intracranial interventions as well as ischemic or hemorrhagic stroke.
Evidence of pre-existing major health conditions, such as cancer, hematological, renal, hepatic, or coronary disease, psychiatric disorders, diabetes, myocardial infarction or other known heart diseases, rheumatoid arthritis, epilepsy, evidence of degenerative or inflammatory diseases affecting the nervous system (e.g., Alzheimer, Parkinson). Patients with well-controlled diabetes and hypertension were included if there was no evidence of secondary damage to major organs.
Patients under chronic treatment with cortisone, Ca^{+}-channel blockers, antidepressants, antipsychotic drugs, or nootropic molecules.
Any neurological or non-neurological condition independent from TBI that might influence the functional outcome or other efficacy outcome measures.
Injury of writing hand influencing cognitive or other outcome measures, in the investigator's judgment.
Clear clinical signs of intoxication influencing the evaluation, in the investigator's judgment.
Signs of addiction, in the investigator's judgment.
Patients with penetrating brain injury.

Primary outcome ensemble

The primary multidimensional outcome ensemble at day 30 and day 90 in the recovery phase consists of eight dimensions, comprising 13 single analysis variables (five of the eight dimensions comprising two independent subscales each):

1. Glasgow Outcome Scale-Extended (GOS-E) [12, 13], all visits;
2. Early Rehabilitation Barthel Index [14], all visits;
3. Mini-Mental State Examination (MMSE) [15], all visits;
4. PSI (Processing Speed Index, Wechsler adult intelligence scale) [16–19], 2 subscales, all visits;
5. Stroop Color-Word Test—Victoria Version (VST) [20], two subscales, all visits;
6. Digit Span (Wechsler adult intelligence scale) [16], two subscales, day 30, day 90;
7. Color Trails Test [21], two parts, day 30, day 90;
8. Hospital Anxiety and Depression Scale [22, 23], two subscales, day 30, day 90.

An ensemble of the first five outcome scales was tested at day 10 after brain injury (i.e., neuroprotection phase) separately by a multivariate, directional test approach, reflecting the global status of patients at this early point in time after TBI.

Safety criteria were vital signs (blood pressure, heart rate, respiration rate, body temperature, weight), electrocardiogram, laboratory tests (hematology, blood chemistry, urinalysis), neurological evaluation (mental status, language, speech, cranial nerves, motor system, muscle stretch reflexes, grading reflexes, sensation, involuntary movements), physical evaluation, concomitant medication, and adverse events.

The Baseline Prognostic Risk Score (BPRS), a highly validated and weighted prognostic scale, was calculated to obtain a measure of heterogeneity of the study population [24]. This scale includes the criteria recommended by the IMPACT study group [25] and has seven outcome predictors obtained before randomization: age, motor score, computed tomography classification, pupillary reactivity, hypoxia, hypotension, and traumatic subarachnoid hemorrhage.

Definition of study population groups

The intention-to-treat (ITT) population, used for all efficacy analyses, included patients who had at least one dose of

medication and at least one post-baseline observation of at least one primary efficacy criterion. A sensitivity analysis was performed for a per-protocol (PP) data set as an exploratory approach. The PP population included all patients who were eligible for ITT evaluation and who additionally did not show significant protocol deviations. The safety population included all patients who had at least one dose of study medication and one subsequent contact with study investigators.

Statistical analysis

A non-parametric assessment of treatment effects that is independent of data type and sample distribution was used as the primary analysis method, in order to minimize unrealistic assumptions about the distribution of data, such as normality or homogeneity of variances [26]. The multivariate analysis was performed using the Wei-Lachin procedure [27, 28], a multivariate generalization of the Wilcoxon-Mann-Whitney test, which takes into account the correlation among univariate Mann-Whitney tests for each outcome, to produce an overall average estimate of clinical status that is suitable to test for differences between treatment groups.

The principle of a priori ordered hypotheses was employed to control for multiplicity due to multiple time points (days 90, 30, 10). According to the ICH Guideline E9, the results are provided as *P* values and as effect size measures with corresponding confidence intervals [29]. The relevant benchmarks for the Mann-Whitney statistic are 0.29 (large inferiority), 0.36 (medium-sized inferiority), 0.44 (small inferiority), 0.5 equality, 0.56 (small superiority), 0.64 (medium-sized superiority), and 0.71 (large superiority) [30].

The worst rank imputation was introduced to address missing values for outcome scales due to patients unable to complete due to death or TBI-related neurological reasons. For missing data not related to TBI and due to injuries in other anatomical regions, an LPCF (Last Percentile Carried Forward) replacement was performed. If no previous follow-up measurement existed, the outcome scale remained missing as defined in the protocol, except for deceased patients. In the case of stable low GOSE scores at visit 1 and visit 3 (severe disability or worse), missing values at last visit for any reason except death were imputed with LOCF (Last Observation Carried Forward) instead of LPCF in order to prevent bias.

Sample size calculation

The sample size was determined based on one-sided type I error defined as alpha = 0.05, 90% statistical power, a two-stage procedure according to Bauer and Köhne [31–33], Mann-Whitney statistic (MW) = 0.64 ("medium-sized" difference [34]). Estimated correlations among the single outcome scales included in the global statistics were also considered for sample size determination based on results of the Traumatic Brain Injury Trials Group [35], along with recommendations for additional scales introduced by the CAPTAIN Trial Advisory Board [36]. Non-parametric sample size calculations within the framework of a multiple outcome approach were performed applying the validated software Nnpar 1.0 from idv Data Analysis and Study Planning. While a total of 127 patients were required under the above design assumptions for days 90/30, a total of 140 patients were required for day 10 to achieve at least 90% power for all multivariate tests at all points in time.

Results

The CAPTAIN II trial enrolled a total of 142 patients (of 187 patients screened) who received at least one dose of study treatment (Fig. 1).

The primary confirmatory analysis set (ITT population) comprises 139 cases that underwent formal analysis. Three patients were excluded from all efficacy analyses due to lack of any follow-up data. Treatment groups registered excellent comparability as indicated by baseline characteristics of the ITT population, as described in Table 2.

Primary hypothesis no. 1 (multidimensional ensemble at day 90)—confirmatory analysis

At day 90, the combined effect size for the multivariate ensemble was between the benchmarks for a "small" and "medium-sized" superiority ($MW_{combined} = 0.59$), with all 13 single outcome scales and subscales indicating the superiority of Cerebrolysin as compared to placebo. For the multivariate ensemble, the difference between the two treatment groups is statistically significant ($P_{Wei\text{-}Lachin} = 0.0119$, two-sided; 95% CI 0.52 to 0.66). Additionally, six outcome scales were stand-alone statistically significant, as illustrated by Fig. 2: Processing Speed Index ($P_{Wei\text{-}Lachin} = 0.0155$, two-sided; MW = 0.62; 95% CI 0.52 to 0.72), Stroop Word/Dots Interference ($P_{Wei\text{-}Lachin} = 0.0005$, two-sided; MW = 0.67; 95% CI 0.57 to 0.76), Digit Span Forward ($P_{Wei\text{-}Lachin} = 0.03$, two-sided; MW = 0.61; 95% CI 0.51 to 0.71), Digit Span Backward ($P_{Wei\text{-}Lachin} = 0.0029$, two-sided; MW = 0.65; 95% CI 0.55 to 0.75), Color Trails Test 1 ($P_{Wei\text{-}Lachin} = 0.0235$, two-sided; MW = 0.61; 95% CI 0.51 to 0.71), and HADS—Depression sumscore ($P_{Wei\text{-}Lachin} = 0.0026$, two-sided; MW = 0.65; 95% CI 0.55 to 0.74).

The per-protocol sensitivity analysis of the primary multidimensional outcome ensemble well supported the results of the ITT analysis, showing a statistical significant superiority of Cerebrolysin ($P_{Wei\text{-}Lachin} = 0.0058$, $MW_{combined} = 0.60$ (95% CI 0.53 to 0.68); Fig. 3), with effect sizes of six single outcome showing stand-alone statistical significance.

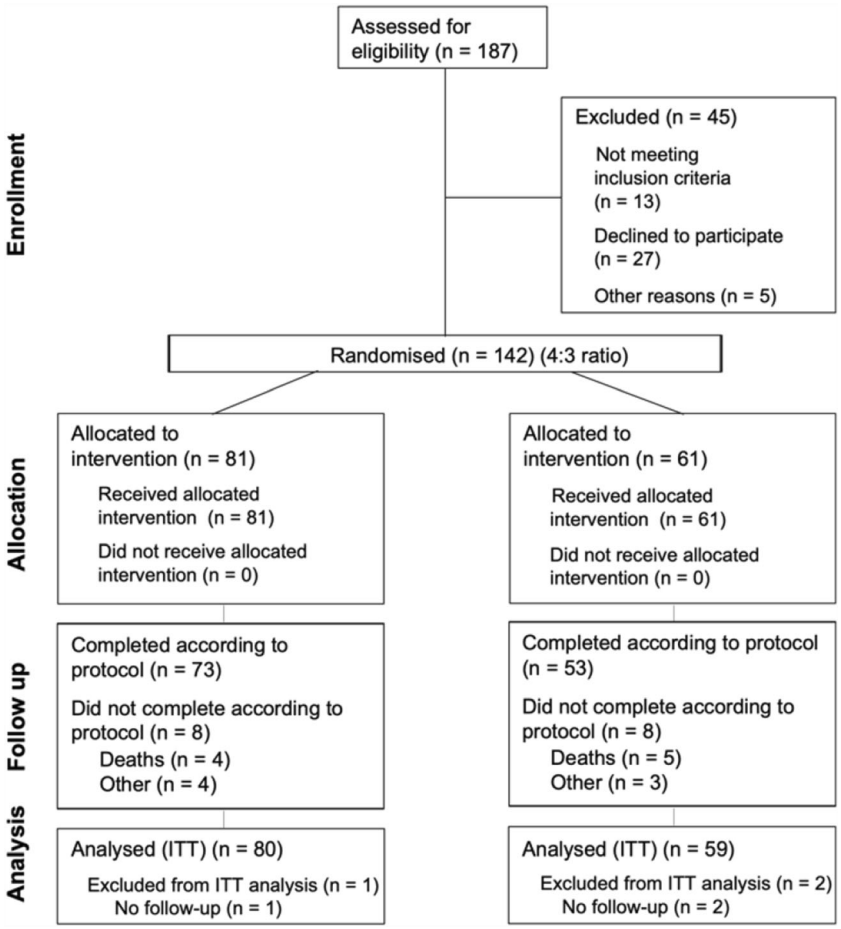

Fig. 1 Flow diagram of patients in the CAPTAIN II trial

Primary hypothesis no. 2 (multidimensional ensemble at day 30)—confirmatory analysis

The combined effect size for the primary multivariate ensemble at day 30 indicates small superiority of Cerebrolysin in the ITT population ($MW_{combined}$ = 0.57), and a more than "small superiority" in the PP population, with all 13 single outcome scales and subscales showing superiority of Cerebrolysin. In the multivariate outcome ensemble, the difference between the two treatment groups just missed statistical significance in the ITT analysis ($P_{Wei\text{-}Lachin}$ = 0.0508, two-sided; 95% CI 0.49 to 0.65; Fig. 4), however, showed statistical significance in the PP analysis ($P_{Wei\text{-}Lachin}$ = 0.0236, two-sided; 95% CI 0.52 to 0.67; Fig. 4). A stand-alone statistically significant superiority of

Table 2 Demographic baseline characteristics for the ITT study population

Indicator	Total, n = 139	Cerebrolysin, n = 80	Placebo, n = 59
Male sex, number (%)	123 (88.5)	72 (90.0)	51 (86.4)
Mean age, years (SD)	47.4 (17.3)	46.4 (17.1)	48.8 (17.6)
Mean BPRS, (SD)	2.6 (1.8)	2.6 (1.8)	2.6 (1.8)
Mean AIS face, (SD)	1.3 (0.5)	1.2 (0.4)	1.3 (0.5)
Mean AIS other regions (maximum score), (SD)	1.3 (0.4)	1.3 (0.5)	1.2 (0.4)
Mean GCS total score at admission, (SD)	10.4 (1.4)	10.2 (1.5)	10.6 (1.3)
Mean GCS motor score at admission, (SD)	4.6 (0.6)	4.6 (0.6)	4.7 (0.5)
Mean GCS total score pre-treatment, (SD)	10.9 (1.4)	10.8 (1.4)	11.0 (1.3)
Mean GCS motor score pre-treatment, (SD)	4.8 (0.4)	4.8 (0.6)	4.8 (0.4)

BPRS Baseline Prognostic Risk Score, *GCS* Glasgow Coma Scale, *AIS* Abbreviated Injury Scale, *SD* standard deviation

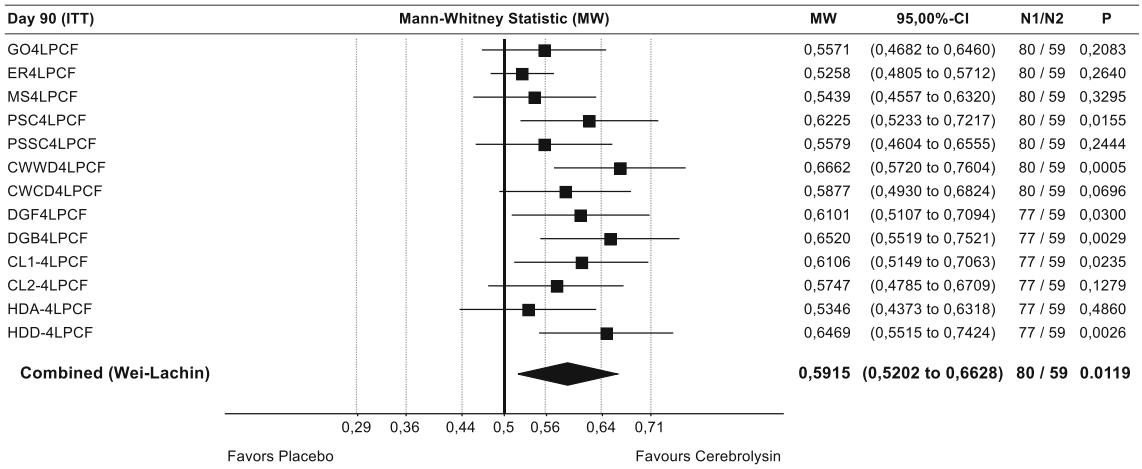

Fig. 2 Confirmatory multivariate outcome ensemble at day 90 (early recovery phase), Wei-Lachin procedure, intention-to-treat (ITT). MW Mann-Whitney, CI confidence interval, N1 valid number Active Treatment, N2 valid number placebo, GO4LPCF Glasgow Outcome Scale Extended (GOS-E), ER4LPCF Early Rehabilitation Barthel Index, MS4LPCF Mini-Mental State Examination, PSC4LPCF Processing Speed Index (PSI), Digit Symbol Coding, PSSC4LPCF Processing Speed (PSI) Symbol Search, CWWD4LPCF Stroop (VST) Word/Dots Interference, CWCD4LPCF Stroop (VST) Color-Word/Dots Interference, DGF4LPCF Digit Span Digit Forward Test, DGB4LPCF Digit Span Digit Backward Test, CL1-4LPCF Color Trails Test 1, CL2-4LPCF Color Trails Test 2, HDA-4LPCF HADS: Anxiety Sumscore, HDD-4LPCF HADS: Depression Sumscore; visit no. 4 = day 90

Cerebrolysin was observed in four individual outcomes (ITT population): Stroop Word/Dots Interference ($P_{\text{Wei-Lachin}} = 0.0073$, two-sided; MW = 0.63; 95% CI 0.53 to 0.72), Digit Span Forward ($P_{\text{Wei-Lachin}} = 0.0304$, two-sided; MW = 0.61; 95% CI 0.51 to 0.71), Digit Span Backward ($P_{\text{Wei-Lachin}} = 0.0122$, two-sided; MW = 0.63; 95% CI 0.53 to 0.73), and HADS Depression Sumscore ($P_{\text{Wei-Lachin}} = 0.0263$, two-sided; MW = 0.61; 95% CI 0.51 to 0.70), as illustrated by Fig. 4.

In the PP population, stand-alone statistical significance was observed in 6 outcome scales (Fig. 5).

Primary hypothesis no. 3 (multidimensional ensemble at day 10)—exploratory analysis

Since the primary hypothesis no. 2 (day 30) just missed statistical significance ($P = 0.0508$, ITT), the result of the a priori ordered hypothesis no. 3 (day 10) is to be interpreted in an

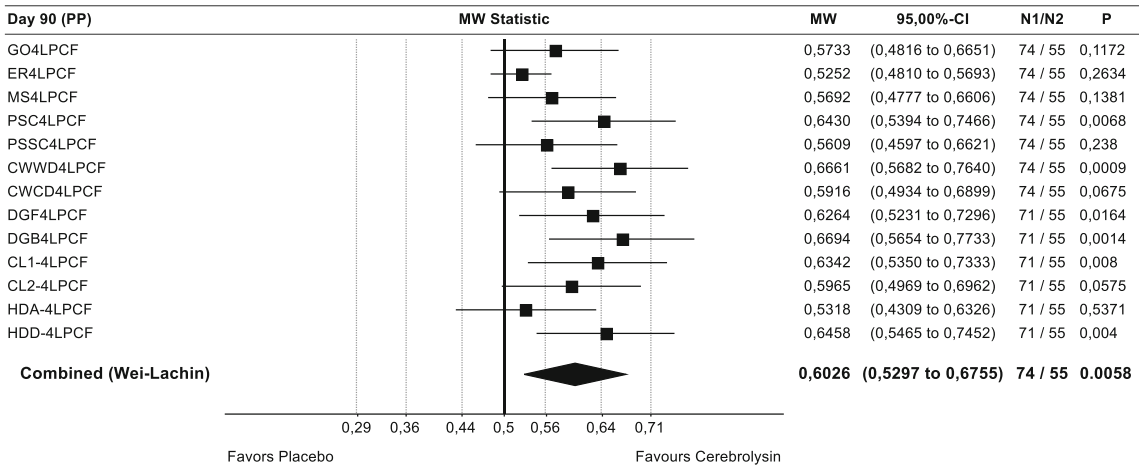

Fig. 3 Multivariate outcome ensemble at day 90 (early recovery phase), Wei-Lachin procedure, per-protocol sensitivity analysis (PP). MW Mann-Whitney, CI confidence interval, N1 valid number Active Treatment, N2 valid number placebo, GO4LPCF Glasgow Outcome Scale Extended (GOS-E), ER4LPCF Early Rehabilitation Barthel Index, MS4LPCF Mini-Mental State Examination, PSC4LPCF Processing Speed Index (PSI), Digit Symbol Coding, PSSC4LPCF Processing Speed (PSI) Symbol Search, CWWD4LPCF Stroop (VST) Word/Dots Interference, CWCD4LPCF Stroop (VST) Color-Word/Dots Interference, DGF4LPCF Digit Span Digit Forward Test, DGB4LPCF Digit Span Digit Backward Test, CL1-4LPCF Color Trails Test 1, CL2-4LPCF Color Trails Test 2, HDA-4LPCF HADS: Anxiety Sumscore, HDD-4LPCF HADS: Depression Sumscore; visit no. 4 = day 90

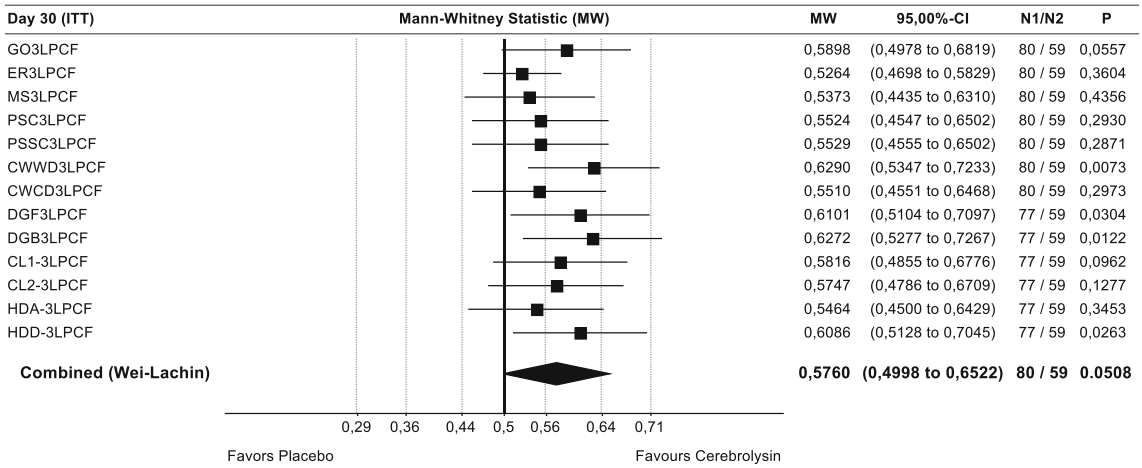

Fig. 4 Confirmatory multivariate outcome ensemble at day 30 (early recovery phase), Wei-Lachin procedure, intention-to-treat (ITT). MW Mann-Whitney, CI confidence interval, N1 valid number Active Treatment, N2 valid number placebo, GO3LPCF Glasgow Outcome Scale Extended (GOS-E), ER3LPCF Early Rehabilitation Barthel Index, MS3LPCF Mini-Mental State Examination, PSC3LPCF Processing Speed Index (PSI), Digit Symbol Coding, PSSC3LPCF Processing Speed (PSI) Symbol Search, CWWD3LPCF Stroop (VST) Word/Dots Interference, CWCD3LPCF Stroop (VST) Color-Word/Dots Interference, DGF3LPCF Digit Span Digit Forward Test, DGB3LPCF Digit Span Digit Backward Test, CL1-3LPCF Color Trails Test 1, CL2-3LPCF Color Trails Test 2, HDA-3LPCF HADS: Anxiety Sumscore, HDD-3LPCF HADS: Depression Sumscore; visit no. 3 = day 30

exploratory manner. The combined effect size for the multivariate ensemble at day 10 was between the benchmarks for a small and medium-sized superiority of Cerebrolysin (MW = 0.54), with six out of the seven single outcome scales or subscales showing the superiority of Cerebrolysin. For the multivariate ensemble, the difference between the two treatment groups was statistically not significant (ITT: $P_{\text{Wei-Lachin}} = 0.22$, two-sided; 95% CI 0.47 to 0.62; PP: $P_{\text{Wei-Lachin}} = 0.13$, two-sided; 95% CI 0.48 to 0.64; corresponding figure available in Supplementary Materials).

Safety and tolerability

The safety population includes all 142 treated patients (placebo 61 patients, Cerebrolysin 81 patients; based on 3:4 ratio of randomization). Adverse events were assessed at each follow-up visit. Altogether, 108 out of 142 patients of the safety population (76.05%) suffered 319 adverse events. Sixty-two patients experienced at least one adverse event out of 81 patients (76.54%) of the Cerebrolysin group and by 46 patients out of 61 patients (75.41%) of the placebo group. The

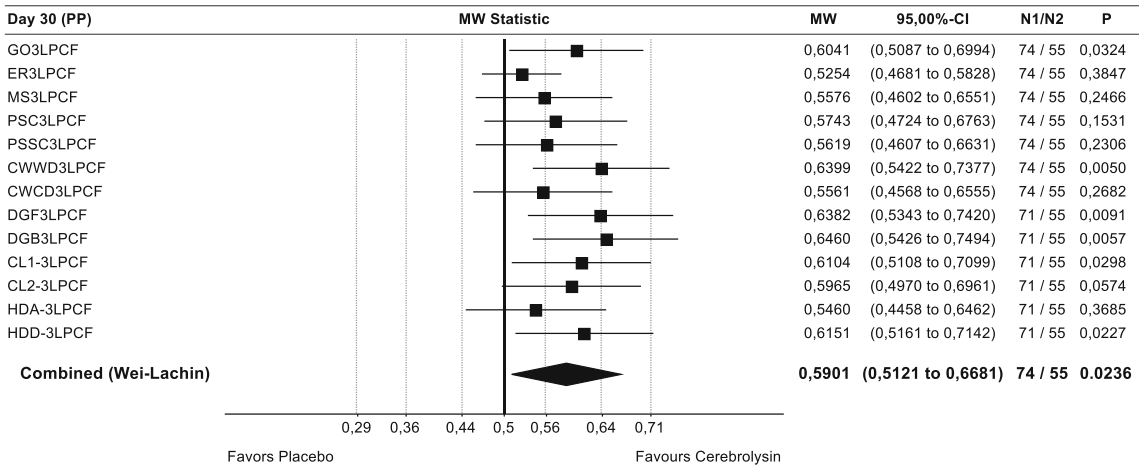

Fig. 5 Multivariate outcome ensemble at day 30 (early recovery phase), Wei-Lachin procedure, per-protocol sensitivity analysis (PP). MW Mann-Whitney, CI confidence interval, N1 valid number Active Treatment, N2 valid number placebo, GO3LPCF Glasgow Outcome Scale Extended (GOS-E), ER3LPCF Early Rehabilitation Barthel Index, MS3LPCF Mini-Mental State Examination, PSC3LPCF Processing Speed Index (PSI), Digit Symbol Coding, PSSC3LPCF Processing Speed (PSI) Symbol Search, CWWD3LPCF Stroop (VST) Word/Dots Interference, CWCD3LPCF Stroop (VST) Color-Word/Dots Interference, DGF3LPCF Digit Span Digit Forward Test, DGB3LPCF Digit Span Digit Backward Test, CL1-3LPCF Color Trails Test 1, CL2-3LPCF Color Trails Test 2, HDA-3LPCF HADS: Anxiety Sumscore, HDD-3LPCF HADS: Depression Sumscore; visit no. 3 = day 30

differences between the two treatment groups can easily be explained by random variation (RR = 1.02, 95% CI 0.84 to 1.22, $P = 0.88$, safety population).

The most common AE was leukocytosis (20), with 13 cases in the Cerebrolysin group and 7 cases in the placebo group. The statistical test shows that the differences concerning leukocytosis can easily be explained by random fluctuation (RR = 1.4, 95% CI 0.59 to 3.29, $P = 0.44$, safety population). Overall, 13 serious adverse events were reported, out of which 5 for 5 patients in the Cerebrolysin group and 8 for 8 patients in the placebo group (RR = 0.47, 95% CI 0.16 to 1.37, $P = 0.17$). Serious adverse events were all unrelated. There were altogether nine fatal adverse events: 4 in the Cerebrolysin group and 5 in the placebo group (RR = 0.60, 95% CI 0.17 to 2.15, $P = 0.43$).

Discussion

The CAPTAIN II trial shows that after moderate to severe TBI, treatment with Cerebrolysin improves global outcome at 90 days as compared to placebo, confirming results from a previous study performed on a sample of Asian patients [37]. A multidimensional outcome ensemble comprising eight domains measuring global outcome, cognitive speed, attention, and depression was used in our study. Besides an overall effect for the total multivariate ensemble favoring Cerebrolysin over placebo, a statistically significant positive effect on six individual outcome scales was found 90 days after baseline.

The pathway that has led to the hypothesis that Cerebrolysin may enhance recovery from brain damage after TBI and the clinical trial design started in 2003, when small exploratory studies demonstrated positive effects of Cerebrolysin on cognition, clinical outcome and EEG measures, in patients after TBI [38–40]. Various retrospective cohort studies [7, 41] suggested a potential beneficial effect of Cerebrolysin. A large cohort study from 2015, which enrolled 615 TBI patients demonstrated better GOS and modified Rankin Scale scores in patients treated with Cerebrolysin as compared to controls at 10 days after injury in mild TBI and at 10 and 30 days in moderate to severe TBI [42].

Rat models for TBI have shown a possible beneficial potential of Cerebrolysin in improving cognitive performance by reducing amyloid precursor protein levels, astrogliosis, and by promoting neurogenesis in the dentate gyrus [43]. In addition, Cerebrolysin may reduce functional deficits and modify blood-cerebrospinal fluid barrier permeability and brain pathology after TBI in rats [44]. Animal studies have also brought forward knowledge regarding dose-response, suggesting the potential of the multimodal biological agent in mild TBI [45], as subsequently confirmed in a clinical trial [11], and various innovations in administration and delivery, such as the aid of polylactic-co-glycolide nanoparticles [46].

A systematic review published in 2016 initially introduced nitric oxide synthase inhibitor, statins, *N*-acetyl cysteine, Enzogenol, and Cerebrolysin as neuroprotective options for pharmacologic intervention in improving functional outcome after TBI [47]. Two years later, El Sayed et al. published a meta-analysis of Cerebrolysin, citicoline, and piracetam, resulting in substantial superiority of the former that was reflected in three-fold cognitive improvement and favorable GOS score [48]. The most recent meta-analysis from 2018 performed exclusively on Cerebrolysin concludes that the agent improves functional outcome for patients after TBI as measured by GOS and mRS but highlights the major limitation of current existing evidence: heavy reliance on cohort studies and absence of clinical trials [10].

At the time when the CAPTAIN I trial protocol was published [36], clinical trials had critical strategic shortcomings in methodological approach, as highlighted by the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) in TBI [5]. Most importantly, therapeutic paradigms focused solely on suppressive neuroprotective drugs instead of exploring pathways for neurological recovery. The purpose of the CAPTAIN trial series was to address these pitfalls by investigating a multimodal neuroprotective and neuroregenerative drug using a multidimensional outcome ensemble approach.

As a complex biological agent with unique pharmacologic properties, Cerebrolysin has a truly multimodal mechanism of action that mirrors endogenous defense responses in the brain, allowing anti-correlated transition from immediate neuroprotection processes that limit impairment to profound and long-term neurorecovery by promoting neurotrophicity, neuroplasticity, and neurogenesis [49].

The CAPTAIN trials were the first randomized clinical studies that used a true multidimensional evaluation of TBI outcome based on full outcome scales [37]. After careful consideration of several statistical methods available to compare two groups concerning more than one outcome [27, 35, 50–55], following state-of-the-art recommendations [25, 56, 67], we chose a robust, non-parametric, correlation-sensitive multidimensional approach for outcome assessment and classification, based on the Wei-Lachin pooling procedure, which is a generalization of the well-known Wilcoxon-Mann-Whitney test. The first study to follow this line of inquiry was the CAPTAIN I trial, which suggested beneficial effects of Cerebrolysin in moderate-to-severe TBI, highlighting the need to replicate these results on a larger sample [37].

With excellent baseline comparability between groups (mean age = 47.4, mean admission GCS = 10.4, and mean Baseline Prognostic Risk Score = 2.6), the results of the CAPTAIN II trial confirm the beneficial effects and the safety of Cerebrolysin of the first trial in the series [37]. While

previous studies used Functional Independence Measure [8], GOS and mRS [10] for appraising global functional status, and only Mini-Mental State Examination and Cognitive Abilities Screening Instrument scores [11] for cognitive assessment, our ensemble of eight full outcome scales offers a much more methodical and comprehensive view of the global status of patients after TBI, as well as a better quantification of potential intervention effects.

By using the extended version of the GOS, we gain higher sensitivity to detect minor but relevant changes in outcome without losing the reliability of rating [57]. The Early Rehabilitation Barthel Index complements the ensemble by introducing relevant functional aspects that may easily differentiate between patients in different phases of rehabilitation [58]. The five scales of CAPTAIN II used to assess cognitive impairment are very much relevant for several different cognitive domains, such as central processing speed [17], selective attention [20], working memory [16], or attention control processing [21].

Although statistically significant in the first primary endpoint (day 90), the agent did not reach statistical significance in the very early neuroprotection phase (day 10). A potential explanation for this finding is that some neuropsychological scales show reduced sensitivity in the acute phase of TBI [59], and other highly responsive neuropsychological scales were assessed at day 30 and day 90 only. Furthermore, several additional confounding factors may influence the patient's status in this highly dynamic early phase after trauma, enhancing overall heterogeneity at day 10.

The most important effect of Cerebrolysin was observed at the first primary study endpoint (day 90). With all the scales showing superiority of the agent and a statistically significant difference between groups, the result confirms its capacity to promote neurorecovery, stimulating natural endogenous processes in the brain, like neurogenesis and neuroplasticity. Moreover, the stand-alone statistically significant superiority of the agent for six outcome scales consolidates this result, with a "small" to "medium-size" effect for Processing Speed Digit Symbol Coding, Digit Span Digit Forward Test, and Color Trails Test 1 and a "medium" to "large-size" effect for Stroop Word/Dots Interference, Digit Span Digit Backward Test, and HADS Depression sumscore.

It is important to note that in this study, performance and emotional state outcome measures were applied. This approach may be complemented in the future by measures which evaluate subjective health-related quality of life, such as the QOLIBRI instruments [60–62], in order to facilitate treatment effectiveness measurement from the patient's perspective.

The main limitations of this trial are its monocentric design, and male gender dominance among participants, which is somewhat to be expected in TBI. Study findings must be appraised and aggregated in conjunction with existing literature, as to improve the overall level of insight regarding therapeutic options for TBI patients.

Conclusion

Looking at the current horizon of pharmacologic intervention for patients after moderate-to-severe TBI, recent clinical trials continue to focus on suppressive, neuroprotective treatment paradigms, based on drugs with monomodal mechanisms of action [56, 63–65]. The CAPTAIN II trial, in line with existing literature, confirms the benefits of Cerebrolysin in moderate to severe TBI, consolidating the case for the use of the multimodal agents and the multidimensional approach in clinical research.

Compliance with ethical standards CAPTAIN II, a single-center, prospective, randomized, double-blind, placebo-controlled clinical trial, was approved by the Ethics Committee of the University of Medicine and Pharmacy in Cluj-Napoca, Romania (No. 714/07.03.2013). A full study protocol is available in the ISRCTN registry (No. 17097163).

Conflict of interest Authors of the manuscript report being members in Advisory Board of the CAPTAIN I trial.

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