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1. Cerebrolysin after moderate to severe traumatic brain injury: prospective meta-analysis of the CAPTAIN trial series.
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ORIGINAL ARTICLE

Cerebrolysin after moderate to severe traumatic brain injury: prospective meta-analysis of the CAPTAIN trial series

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Abstract

Introduction This prospective meta-analysis summarizes results from the CAPTAIN trial series, evaluating the effects of Cerebrolysin for moderate-severe traumatic brain injury, as an add-on to usual care.

Materials and methods The study included two phase IIIb/IV prospective, randomized, double-blind, placebo-controlled clinical trials. Eligible patients with a Glasgow Coma Score (GCS) between 6 and 12 received study medication (50 mL of Cerebrolysin or physiological saline solution per day for ten days, followed by two additional treatment cycles with 10 mL per day for 10 days) in addition to usual care. The meta-analysis comprises the primary ensembles of efficacy criteria for 90, 30, and 10 days after TBI with a priori ordered hypotheses based on multivariate, directional tests.

Results A total 185 patients underwent meta-analysis (mean admission GCS = 10.3, mean age = 45.3, and mean Baseline Prognostic Risk Score = 2.8). The primary endpoint, a multidimensional ensemble of functional and neuropsychological outcome scales indicated a "small-to-medium" sized effect in favor of Cerebrolysin, statistically significant at Day 30 and at Day 90 (Day 30: $MW_{combined} = 0.60$, 95%CI 0.52 to 0.66, $p = 0.0156$; SMD = 0.31; OR = 1.69; Day 90: $MW_{combined} = 0.60$, 95%CI 0.52 to 0.68, $p = 0.0146$; SMD = 0.34, OR = 1.77). Treatment groups showed comparable safety and tolerability profiles.

Discussion The meta-analysis of the CAPTAIN trials confirms the safety and efficacy of Cerebrolysin after moderate-severe TBI, opening a new horizon for neurorecovery in this field. Integration of Cerebrolysin into existing guidelines should be considered after careful review of internationally applicable criteria.

Keywords Moderate-severe traumatic brain injury · Cerebrolysin

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Introduction

Traumatic brain injury (TBI) is a significant public health problem, resulting in death, impairment, and permanent disability in alarmingly large numbers worldwide. TBI requires long-term care, incurring high economic costs to healthcare systems. The USA alone has reported over 2.5 million TBI-related emergency department visits per year. Neurotrauma patients follow the evolution and pathways of chronic diseases, spanning well beyond initial injury [1]. The estimated lifetime cost of TBI in the USA is approximately $76.5 billion (in 2010 dollars) [2].

The last 5 decades have seen major advances and promising approaches in perioperative management strategies of patients with traumatic brain injury (TBI), as reflected by our means to avoid or minimize life-threatening complications, based on evidence-based national and international guidelines in conjunction on acute care and neurorehabilitation [3]. Relatively new is the concept of the so-called in-hospital early (acute) neurorehabilitation (ENR), scientifically proven for brain damage and recovery. Since every hour counts in post-traumatic brain protection and recovery, ENR has now been accepted and introduced into acute TBI management with promising results in quite a number of developed and developing countries both in the Western countries and in Far East [4]. Experimental animal studies performed on a myriad of drugs have revealed cortical and subcortical effects of brain protection and functional recovery mechanism in neurology and neurosurgery [5]. Our experience goes back to 1970 when treating TBI patients with Apallic syndrome or persistent vegetative state [6, 7], today diagnosed as unresponsive wakefulness syndrome [8], and when in prolonged coma or minimal conscious state.

Nevertheless, pharmacological interventions have failed to show benefits for TBI patients, both due to limited mechanisms of action of tested agents, and some critical methodological flaws related to study design and planning. Monomodal drugs fail to exert effects in both neuroprotection and neurorecovery phases [9]. Moreover, classic TBI clinical trials have used individual, dichotomized outcome scales that do not capture many clinically relevant functional information in survivors of any kind of TBI.

Cerebrolysin is a multimodal neuropeptide drug with proven experimental and clinical effects that promote neuroprotection, functional neuroregeneration, and neurorecovery [10]. The objective of this prospective meta-analysis (PMA) of the CAPTAIN trial series was to evaluate the efficacy and safety of Cerebrolysin for moderate-severe traumatic brain injury (TBI), as an add-on to usual care.

Materials and methods

Prospective meta-analysis (PMA) design

On the basis of identical multidimensional ensembles of efficacy criteria and comparable study designs, a formal meta-analysis of the CAPTAIN I [11, 12] and CAPTAIN II trial [13] was pre-planned under blinded conditions, i.e., before any results of the two studies were known, and executed after completion of the two trials [14]. This PMA was based on the blinded a priori definitions for the nonparametric analysis of the CAPTAIN I study, as well as on the PMA operational details as defined in the "Statistical methodology for pre-planned meta-analysis" section of the CAPTAIN I final statistical analysis plan from June 10, 2016. Individual patient data (IPD) were used for added methodological consistency. Risk of bias, as assessed by means of the Cochrane risk-of-bias tool was low [15, 16]. The per protocol (PP) population was comprised of intention to treat (ITT) patients with significant protocol deviations, not related to death, adverse events, or good recovery.

The primary endpoint of both studies was a multidimensional ensemble of functional and neuropsychological outcome scales. Outcome scale distributions were assumed to present non-normal distribution, outliers, and floor-ceiling effects. Therefore, the robust nonparametric multivariate Wei-Lachin procedure [17, 18] was pre-specified for the IPD analyses. The associated effect size measure is the Mann-Whitney (MW) measure of superiority [19–21], with the following benchmarks: 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) [22].

Handling of efficacy criteria

All efficacy criteria were evaluated as pre-defined for the confirmatory analysis of the two studies:

- Glasgow Outcome Scale-Extended (GOS-E) [23, 24]
- Early Rehabilitation Barthel Index [25]
- Mini-Mental State Examination (MMSE) [26]
- PSI (Processing Speed Index, Wechsler adult intelligence scale—third edition) [27–30], 2 subscales
- Stroop Color-Word Test—Victoria Version (VST) [31], two sub-scales
- Digit Span (Wechsler adult intelligence scale—third edition) [27], two sub-scales
- Finger Tapping Test [32–34] (CAPTAIN I confirmatory ensemble only)
- Color Trails Test [35], two parts
- Hospital Anxiety and Depression Scale [36, 37], two subscales

Death, treatment-emergent adverse events (TEAE), and treatment-emergent serious adverse events (TESAE) were used as safety variables. The main feature for evaluation of baseline comparability of treatment groups was the Baseline Prognostic Risk Score (BPRS) [38, 39]. In addition, Abbreviated Injury Score (AIS) face, AIS other regions, GCS total score, and GCS motor score were used for homogeneity assessment.

In order to identify each type of missing data an identification code was assigned in the CRFs to each outcome scale: "valid," "unable to complete due to TBI-related neurological reasons," "not completed or not valid due to other reasons" [40].Treatment of the different types of missing values was performed according to the identical pre-specifications in the two statistical analysis plans. Missing data was handled using worst rank imputation for patients unable to complete due to death or TBI-related neurological reasons and Last Percentile Carried Forward (LPCF) for missing data not related to TBI and due to injuries in other anatomical regions [41].

The pre-specified sequence of hypotheses for the PMA analysis was a multivariate global test at days 30, 90, and 10 for superiority of Cerebrolysin vs. placebo. The global test at day 10 was a priori ordered as last of the three hypotheses, since important cognitive scales could not be included at such an early point in time (smaller pre-specified outcome ensemble). The meta-analysis was based on the ITT population (one or more treatment doses and one or more post-baseline assessment). As a sensitivity analysis, a per protocol (PP) analysis was performed based on the blinded definitions in the two final SAPs.

Methods of synthesis

Outcomes from two studies, previously combined by means of the multivariate Mann-Whitney (MW) effect size measure [42–44], were synthesized using the Wei-Lachin test of stochastic ordering (one-dimensional test) [45], a maximin efficient robust test (MERT) [42, 46]. Qualitative interaction of the studies was tested using the Gail-Simon test [43].

The Hedges-Olkin fixed effects model [44] and the DerSimonian-Laird random-effects model [47] are also provided as sensitivity analysis. Heterogeneity across studies was assessed using chi-square and I^2 statistics [48]. While all continuous scales were evaluated by means of MW, the post hoc analysis of normalized depression (score 0–7 at day 90) was based on the risk ratio (RR), using a classic fixed effects model for this binary outcome.

The individual patient data for the CAPTAIN trials we used to develop the PMA is available in the Harvard Dataverse [49]. For translational purposes, results were re-expressed by means of well-known effect sizes such as standardized mean difference (SMD) for normal distribution shift and odds ratio (OR) for proportional odds [19]. The associated synthesis was based on the fixed effect model (inverse variance, IV).

Results

A total of 188 patients were randomized (CAPTAIN I: 46 patients, CAPTAIN II: 142 patients), and 185 patients received study medication (safety population $N = 185$). Six patients had no follow-up data at all and were excluded from ITT efficacy analysis (ITT population $N = 179$ patients). Premature discontinuation before the primary endpoint was 15.0% in CAPTAIN I and 9.4% in CAPTAIN II, including 5.0% (CAPTAIN I) and 6.5% (CAPTAIN II) cases of death (ITT population). Thus, the overall rate of non-death-related dropouts was 4.5% (10.0% in CAPTAIN I and 2.9% in CAPTAIN II), which is far below the critical limit of 20%, defined by the American Academy of Neurology for class I evidence-based quality studies [50].The mean age of the patients was 38.1 (CAPTAIN I) and 47.4 (CAPTAIN II) years, the proportion of males was 80 and 88%, and the total GCS scores pre-treatment was 8.9 and 10.9 (ITT population).

Table 1 CAPTAIN I—demographic and medical baseline characteristics (ITT)

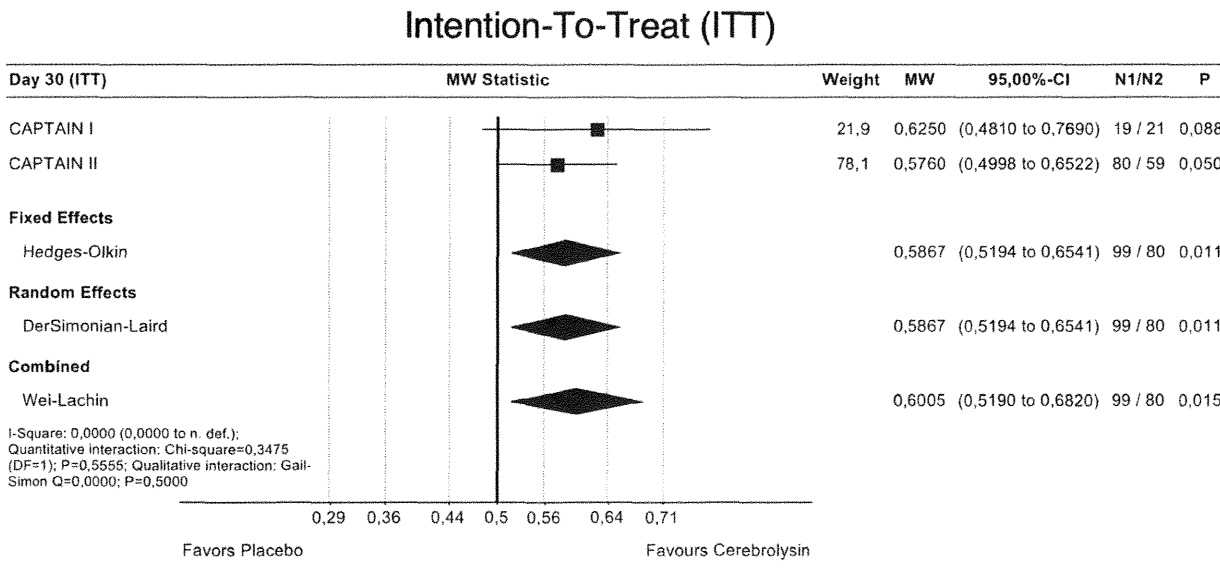
Variable description	Total, $n=40$	Cerebrolysin, $n=19$	Placebo, $n=21$
Male sex, number (%)	32 (80.0)	16 (84.2)	16 (76.2)
Mean age, y, standard deviation (SD)	38.1 (15.8)	38.8 (17.3)	37.3 (15.2)
Mean BPRS, (SD)	3.7 (1.2)	3.8 (1.4)	3.6 (1.1)
Mean AIS Face, (SD)	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)
Mean AIS other regions (maximum score), (SD)	1.4 (0.6)	1.5 (0.6)	1.3 (0.6)
Mean GCS total score at admission, (SD)	9.9 (2.3)	9.5 (2.4)	10.2 (2.3)
Mean GCS motor score at admission, (SD)	5.0 (0.7)	4.9 (0.7)	5.1 (0.7)
Mean GCS total score pre-treatment, (SD)	8.9 (3.4)	8.8 (3.8)	9.0 (3.3)
Mean GCS motor score pre-treatment, (SD)	4.4 (1.6)	4.2 (1.7)	4.5 (1.6)

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

Table 2 CAPTAIN II—demographic baseline characteristics for the ITT study population

Variable description	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



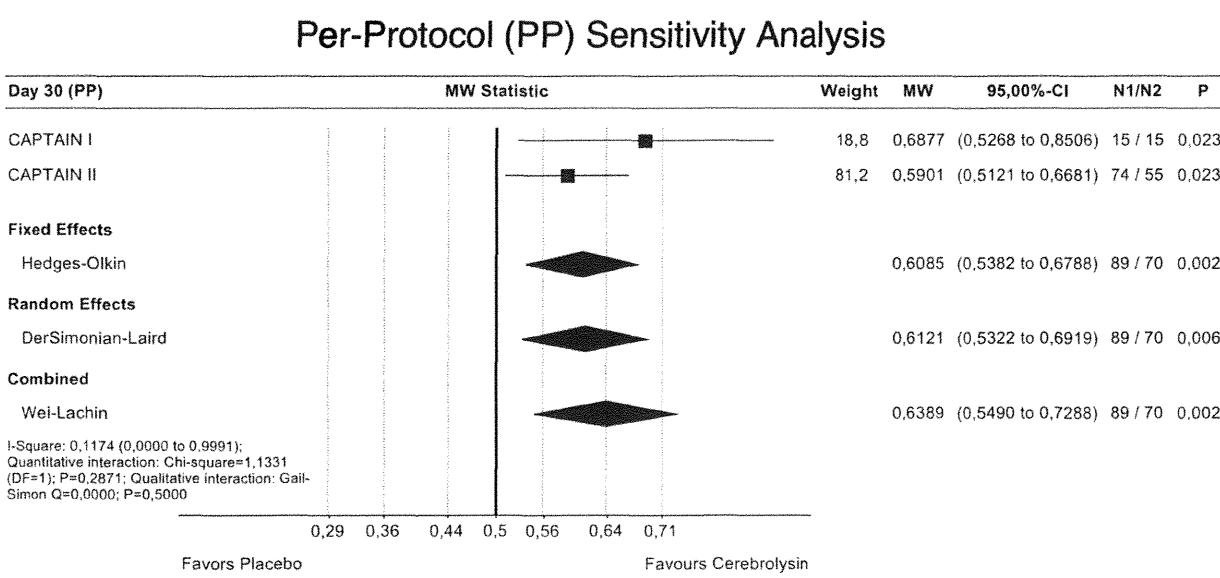
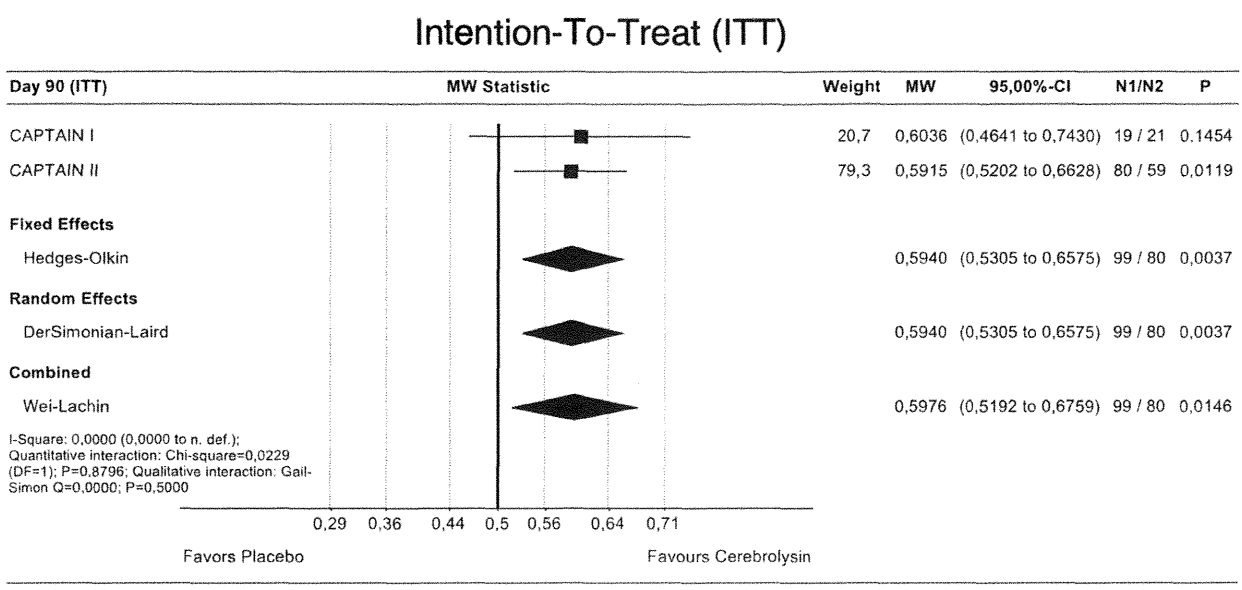


Fig. 1 Confirmatory Multivariate Outcome Ensemble at Day 30 (Early Neurorecovery Phase)

Demographic and clinical characteristics at baseline for the individual trials are described in Tables 1 and 2.

Primary PMA hypothesis no. 1 (multidimensional ensemble at day 30)

At Day 30, the combined effect size for the multivariate ensembles of CAPTAIN I and CAPTAIN II was between the benchmarks for a "small" and "medium-sized" superiority of Cerebrolysin ($MW_{combined} = 0.60$). The difference between the two treatment groups was statistically significant ($P_{Wei\text{-}Lachin} = 0.0156$, two-sided; 95%CI 0.52 to 0.66, ITT population [derived ES: SMD = 0.31, $P = 0.01$, two-sided; 95%CI 0.06 to 0.55; OR = 1.69, $P = 0.01$, two-sided; 95%CI 1.12 to 2.54]). The per-protocol analysis is well supported by the primary result, showing a medium-sized superiority in favor of Cerebrolysin ($MW_{combined} = 0.64$, $P_{Wei\text{-}Lachin} = 0.0024$, two-sided; 95%CI 0.55 to 0.73 [SMD = 0.38, $P = 0.004$, two-sided 95%CI 0.12 to 0.64; OR = 1.93, $P = 0.003$, two-sided; 95%CI 1.26–2.97]). The same applies to the sensitivity analyses based on the classic fixed (Hedges-Olkin) and random effects (DerSimonian-Laird) models. There was no indication for heterogeneity in the trials ($I^2 < 20\%$) (Fig. 1).



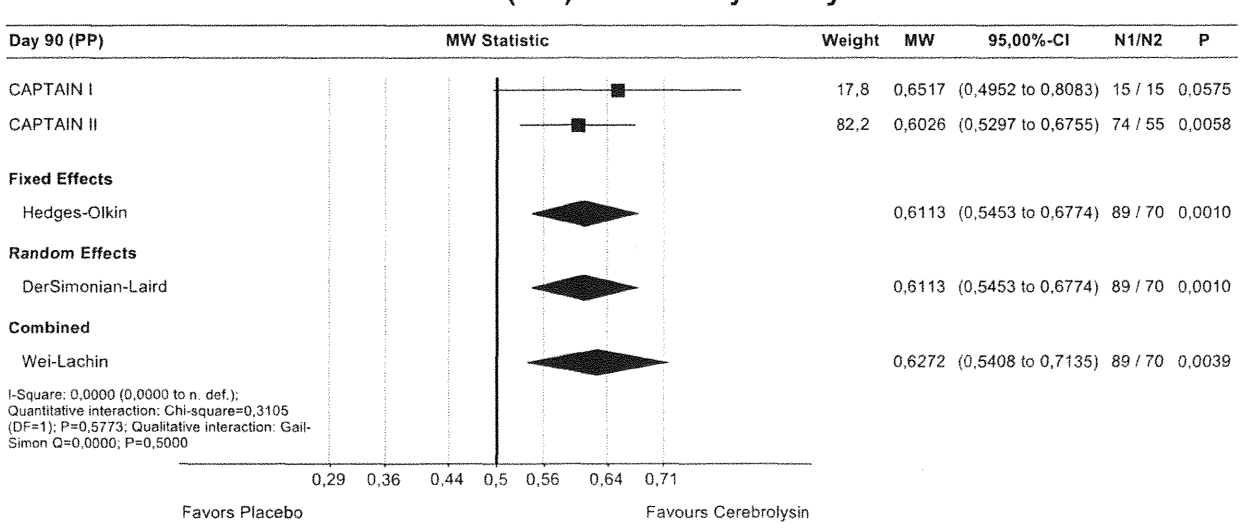
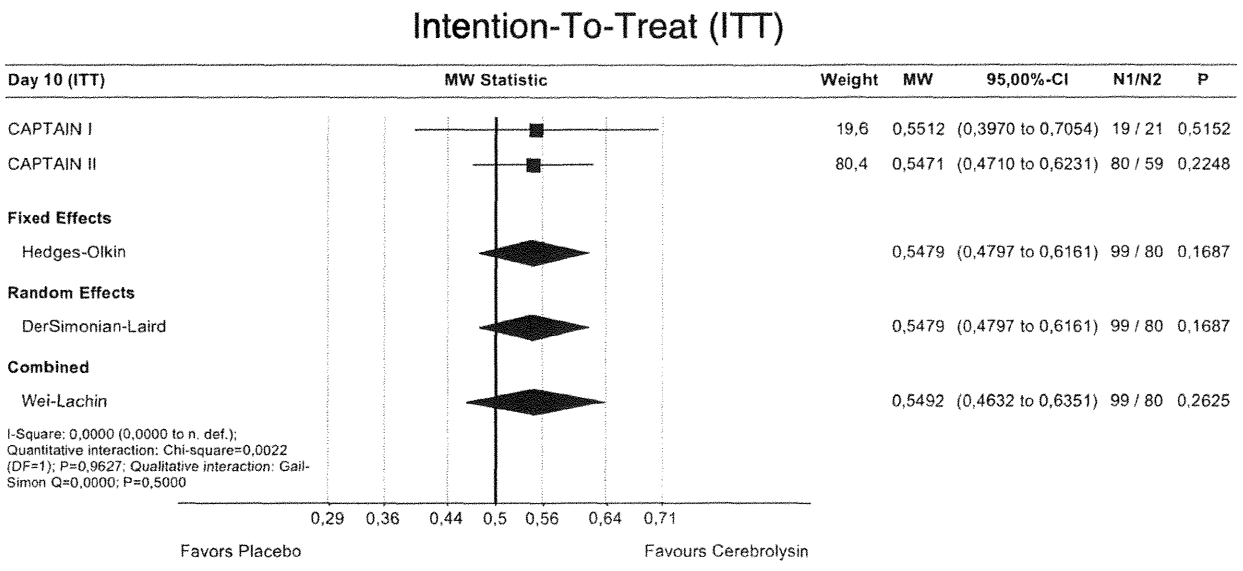


Fig. 2 Confirmatory multivariate outcome ensemble at Day 90 (neurorecovery phase)

Primary PMA hypothesis no. 2 (multidimensional ensemble at day 90)

At Day 90, the combined effect size for the two multivariate ensembles was between the benchmarks for a "small-" and "medium-sized" superiority of Cerebrolysin ($MW_{combined} = 0.60$). The difference between the two treatment groups is statistically significant ($P_{Wei\text{-}Lachin} = 0.0146$, two-sided; 95%CI 0.52–0.68, ITT population [derived ES: SMD = 0.34, P. = 0.004, two-sided; 95%CI 0.11 to 0.57; OR = 1.77, $P = 0.004$, two-sided; 95%CI 1.20 to 2.60]). The per-protocol analysis well supports the primary result, showing a close to medium-sized superiority in favor of Cerebrolysin ($MW_{combined} = 0.63$, $P_{Wei\text{-}Lachin} = 0.0039$, two-sided; 95%CI 0.54–0.71 [SMD = 0.40, $P = 0.001$, two-sided; 95%CI 0.15.

to 0.64; OR = 1.97, P = 0.001, two-sided; 95%CI 1.32–2.95]). The same applies to the sensitivity analyses based on the classic fixed and random effects models. There is no indication for heterogeneity in the trials ($I^2 < 20\%$) (Fig. 2).



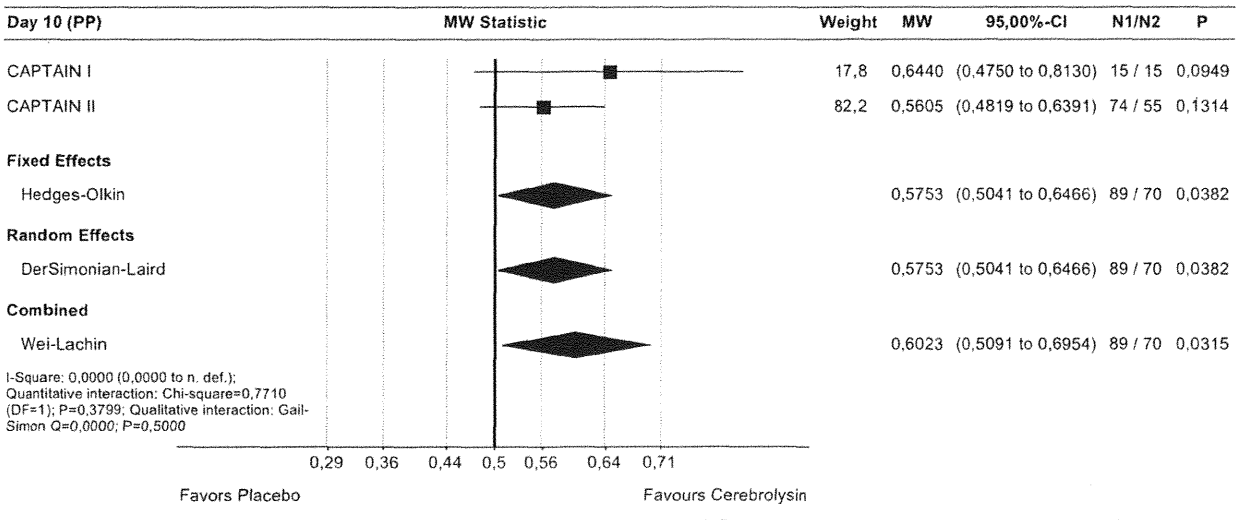


Fig. 3 Confirmatory multivariate outcome ensemble at Day 10 (Neuroprotection Phase)

Primary PMA hypothesis no. 3 (multidimensional ensemble at day 10)

At Day 10, the combined effect size for the two multivariate ensembles shows a slightly less than "small" superiority of Cerebrolysin ($MW_{combined} = 0.55$). The difference between the two treatment groups is statistically not significant ($P_{Wei-Lachin} = 0.2625$, two-sided; 95%CI 0.46–0.64, ITT population [derived ES: SMD = 0.17, $P = 0.17$, two-sided; 95%CI 0.07–0.41; OR = 1.33, P = 0.17, two-sided; 95%CI 0.88 to 2.01]). The per-protocol analysis shows a "small-" to "medium-sized," statistically significant superiority of Cerebrolysin ($MW_{combined} = 0.60$, $P_{Wei-Lachin} = 0.0315$, two-sided; 95%CI 0.51–0.70 [SMD = 0.26, $P = 0.04$, two-sided; 95%CI 0.01–0.52; OR = 1.58, i = 0.04, two-sided; 95%CI 1.02–2.42]). The results of the sensitivity analyses based on the classic fixed and random effects models are similar to the main non-parametric analysis. There is no indication for heterogeneity in the trials ($I^2 < 20\%$) (Fig. 3).

Exploratory post hoc analysis: depression

Depression is one of the most common comorbidities after TBI. We conducted a meta-analysis at 90 days after trauma (last existing visit of the CAPTAIN II trial). For the HADS depression subscale, a more than "medium-sized" (relevant) treatment effect was consistently shown throughout all meta-analytic approaches (MW > 0.64; $P < 0.01$, Fig. 4 [derived ES: SMD = 0.56, $P = 0.0009$, two-sided; 95%CI 0.23–0.89; OR = 2.60, $P = 0.0004$, two-sided; 95%CI 1.53–4.41]). Final normalization of the HADS score (Score 0–7 at Day 90) was found in 70.5% of the Cerebrolysin patients as compared with 39.5% of the placebo patients (RR = 1.89, 95%CI = 1.32 to 2.44, $P = 0.0002$, (Fig. 5). The rate difference of 31% may be regarded as a substantial reduction of the burden of depression of the patients. There was no indication for heterogeneity of the two trials ($I^2 < 20\%$).

Safety and tolerability

The safety population of the two trials includes 185 treated patients (CAPTAIN I: Placebo - 22 patients, Cerebrolysin, 21 patients; 1:1 randomization; CAPTAIN II: Placebo, 61 patients, Cerebrolysin, 81 patients; 3:4 randomization). Adverse events were assessed at each follow-up visit. In the Cerebrolysin groups, 73.5% of the patients experienced at least one adverse event, 7.8% of the patients experienced at least one serious adverse event, and 3.9% of the patients died. In the placebo groups, 73.5% of the patients experienced at least one adverse event, 18.1% of the patients experienced at least one serious adverse event, and 8.4% of the patients died.

As shown in Fig. 6, the group differences regarding serious adverse events just missed statistical significance in favor of Cerebrolysin (RR = 0.46, 95%CI 0.21–1.03, $P = 0.06$). Regarding the number of patients with at least one adverse events, the meta-analysis indicates equality of the groups (RR = 1.0, 95%CI 0.84–1.19, $P = 0.98$), regarding deaths a substantial; however non-significant reduction of deaths in the Cerebrolysin group was found (RR = 0.51, 95%CI = 0.16 to 1.65, $P = 0.26$). There is no indication for heterogeneity in the two trials ($I^2 < 20\%$) (Fig. 6).

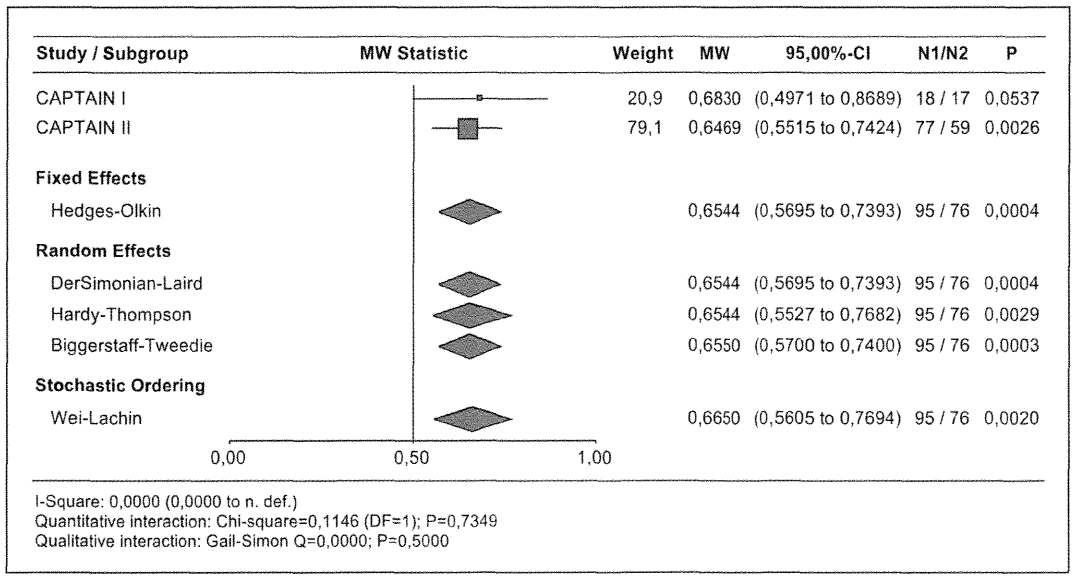


Fig. 4 Depression at Day 90 (Hospital Anxiety and Depression Scale)

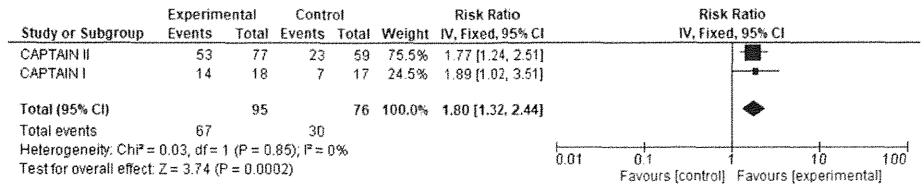


Fig. 5 Normalized Depression at Day 90 (Hospital Anxiety and Depression Scale)

Discussion

The objective of the CAPTAIN I and CAPTAIN II trials was to measure the effect of Cerebrolysin as adjunctive treatment for standard care in eligible individuals after moderate-severe TBI. Cerebrolysin is a biological agent comprised of active fragments of neurotrophic factors of lipid-free from animal proteins, which has been proven to exert a multimodal mechanism of action in stroke and other neurological diseases [51]. The agent promotes the brain's endogenous defense responses, allowing the shift of focus in the recovery process from limiting impairment (neuroprotection) to more long-term mechanisms that involve neurotrophicity, neuroplasticity, and neurogenesis (neurorecovery) [52].

In patients after TBI, Cerebrolysin has previously shown benefits on cognition and clinical outcome [53, 54]. In a 2016 systematic review, Cerebrolysin and several other interventions were presented as treatment options for improving functional outcome after TBI [55]. In a meta-analysis published by El Sayed et al. that included several interventions after TBI, treatment with Cerebrolysin was associated with significant cognitive improvement [56]. Moreover, a meta-analysis concluded that Cerebrolysin improves functional outcomes for patients after TBI, as measured by GOS and mRS. The paper also highlights the major limitation of current existing evidence in the field of TBI pharmacological intervention: heavy reliance on cohort studies and the absence of clinical trials [57].

The meta-analysis of the two CAPTAIN trials confirms the beneficial effects and the safety of Cerebrolysin in patients after moderate to severe TBI. While previous studies used Functional Independence Measures [58] as the GOS and the mRS [59], and the Mini-Mental State Examination and Cognitive Abilities Screening Instrument scores [60] for assessment of cognition, 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.

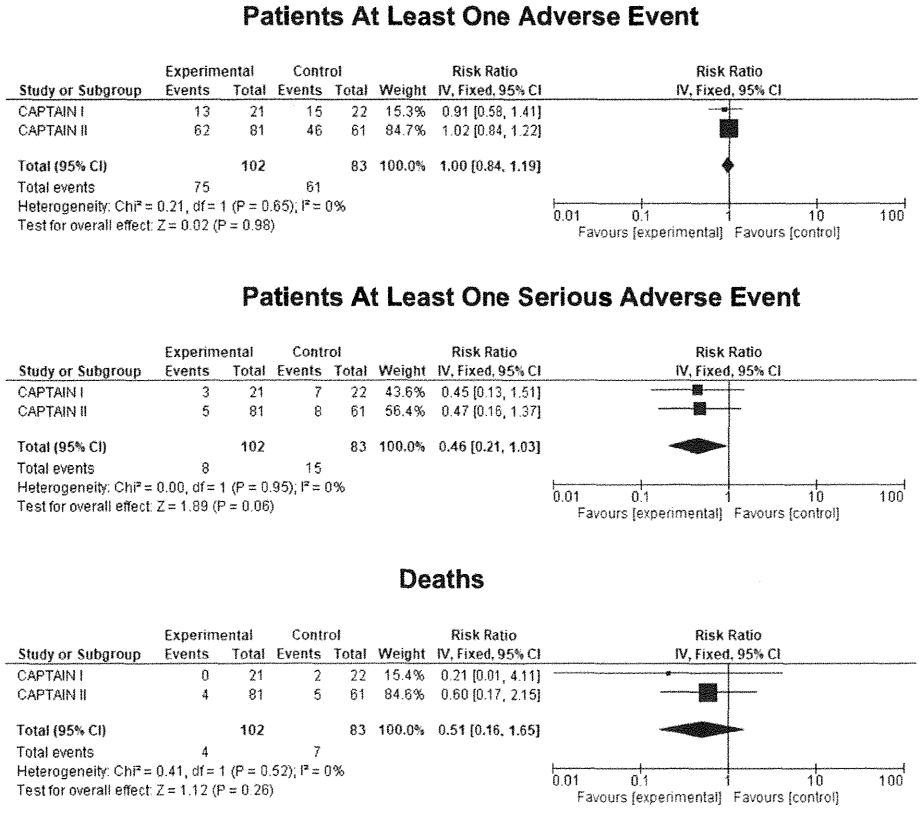


Fig. 6 Safety meta-analyses, fixed effect, risk ratio, safety population

As compared with the conventional GOS, the extended version provides higher sensitivity while maintaining the quality of rating [61]. The scales CAPTAIN used to assess cognitive impairment encompass essential cognitive domains, such as central processing speed [28], selective attention [31], working memory [27], or attention control processing [35]. Both performance and emotional state outcome measures were applied in these trials. Outcome domains such as depression are needed to complement the broad assessment by the GOSE to capture the multifaceted process of neurorecovery after TBI.

The smaller effect size observed in the acute (neuroprotection) phase might be attributed to the low sensitivity of outcome measures in this stage of recovery after TBI [62]. More robust instruments such as the Color Trails Test, Digit Span, or the Hospital Anxiety and Depression Scale were only assessed at Day 30 and Day 90 only. In the period immediately after injury, overall clinical heterogeneity and outcome measurement confounders due to patient impairment potentially render treatment effects less visible at Day 10 (Fig. 3).

The results of this meta-analysis are limited to the defined moderate-severe study population. Patients with mild TBI might react differently to the add-on treatment, the same applies to patients with very severe TBI, i.e., with GCS scores between 3 and 5. Another limitation of the present meta-analysis is the lack of long-term results (e.g., after 1 year). First infusion within 6 h might not be feasible in all local conditions. The same applies to the availability of validated outcome scales in other language regions. Standard of care will surely differ across regions, and low- vs. high-income countries might play an important modifying role with respect to treatment effects. Further studies, with longer duration, are recommended to tighten the present results and to allow broader generalizability.

The meta-analysis of the CAPTAIN trials confirms the safety and efficacy of Cerebrolysin in patients who have suffered moderate to severe TBI, opening a new horizon for neurorecovery in this field. The agent is a good option for the early treatment of primary moderate-severe TBI and should make its way into the existing standards of care, based on current local situations. The integration of Cerebrolysin into existing guidelines should be considered after careful review in accordance with the internationally applicable criteria.

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Compliance with ethical standards

Conflict of interest The CAPTAIN I trial has received an unrestricted research grant from Ever Neuro Pharma GmbH, the manufacturer of Cerebrolysin.

Ethics approval CAPTAIN I: ClinicalTrials.gov (NCT01606111) and local IRB approval.

CAPTAIN II: Ethics Committee of the University of Medicine and Pharmacy in Cluj-Napoca, Romania (No. 714/07.03.2013); ISRCTN registry (No.:17097163).

Consent to participate Investigators obtained written informed consent from all study participants.

Financial disclosure This manuscript was drafted without financial support.

Informed consent Informed consent was obtained from all individual participants included in the study.

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