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Scientific Symposium EVER
Innovative treatment options for traumatic brain injury (TBI)

Satellite Symposium at the 5th EAN Congress
June 29 - July 2, Oslo, Norway

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Program of the symposium

Innovative treatment options for traumatic brain injury (TBI)

Monday, July 1, 2019, 13:45-14:45, Hall B2
Chairman: Erich Schmutzhard, Austria

Welcome speech

Erich Schmutzhard

Department of Neurology, Medical University Innsbruck, Austria

Opening the session, Dr. Schmutzhard highlighted a need for a revision of the diagnostic and therapeutic measures in the field of traumatic brain injury (TBI). This task should be seen in the context of the changing epidemiology patterns observed in various parts of the world. In the Western Hemisphere, it used to be that 20 to 30 years old patients were prevalent while right now the majority of TBI patients belong to the age category of 65 years old and above. Also, the cause of TBI has changed dramatically, with accidental falls prevailing over the road traffic accidents and leisure time-related injuries. Meanwhile, in the lower and middle-income countries, we still see a growing number of young TBI patients injured mainly in road accidents. It is also time now to draw from the experience of the last 30 years of clinical development in order to enhance our therapeutic processes. This should go in parallel with promoting the ever-important preventive measures. The two areas of special interest in the management of moderate-to-severe TBI patients appear to be the intensive care and neuroprotective strategies. At the same time, mild, repetitive TBI attracts increased interest due to its long-term neurological consequences (including a negative impact on social relationships, depression and cognitive function) and high prevalence among the TBI population.

Treatment of TBI with Cerebrolysin enhances neurological and cognitive recovery

Michael Chopp

Department of Neurology, Henry Ford Hospital, Detroit, USA

ABSTRACT:

In this presentation, I will present our preclinical investigations of the treatment of TBI with Cerebrolysin. Double-blind placebo-controlled studies of dose-response and therapeutic window for Cerebrolysin treatment of TBI will be described.

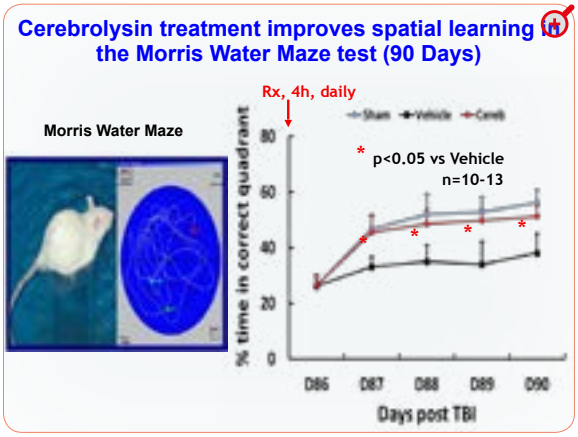
We demonstrate that post-TBI treatment (acute and sub-acute) of multiple models on TBI significantly improve neurological, functional and cognitive outcomes. Our data also provide fundamental insight into the mechanisms by which Cerebrolysin enhances recovery from TBI. Potent pathways of neurovascular protection and remodeling amplified by Cerebrolysin will be presented.

In concern, these protective and restorative mechanisms lead to a profound therapeutic effect of Cerebrolysin for the world`s most prevalent source of neurological dysfunction - TBI.

Dr. Chopp's introduced the audience to the results of his team's recent research conducted in animal models of moderate TBI, with Cerebrolysin as the therapeutic agent. The scope of their ongoing research is comprehensive and includes functional outcomes (motor, somatosensory, learning, memory, spatial orientation, social behavior, anxiety, depression), dose-finding studies, and mechanism of action (at physiological, cellular, and molecular levels). Both TBI and stroke models are being investigated.

Recently, a moderate, closed head injury model was chosen to investigate Cerebrolysin treatment in the context of cognitive functions. This double-blind, randomized study also employed sham and saline controls. Saline or Cerebrolysin (IP) were administered 4 hours post-TBI and then daily for a total of 10 days. The modified Morris Water Maze test was conducted late in the recovery period (from day 86) and served the objective of learning and memory assessment (**Fig. 1a**).

In this experiment, the rats learn to use the external cues in the laboratory to memorize the placement of the hidden (underwater) platform in the pool. After several training sessions, the animals quickly navigate to the invisible platform. Following TBI, the rats lose the ability to recognize the familiar spatial cues and spend much more time swimming around and looking for the platform. The effect of the treatment with Cerebrolysin in this experimental setup was quite dramatic. The animals performed identically to normal, sham animals (those without TBI). In another experiment, a Three-Chamber Test was employed. The rats were positioned to interact with each other and explore novelty, which is a deeply rooted and spontaneous social behavior. The healthy rats spent most of the time socializing with strangers. After TBI, (saline-treated control group), their interest in social interaction and exploration was significantly inhibited. Again, treatment with Cerebrolysin resulted in full recovery of normal social behavior, (**Fig. 1b**).



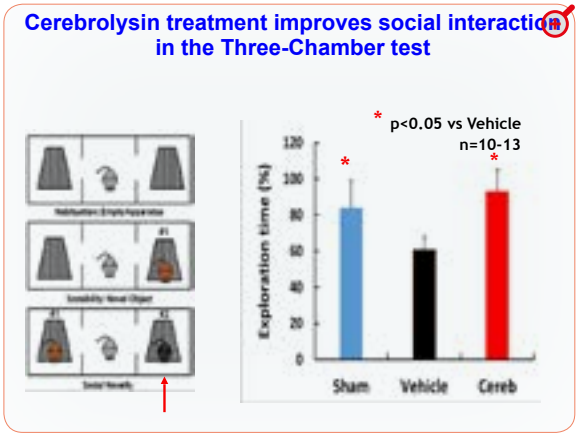


Fig. 1a **Fig. 1b**

In a moderate closed head injury model, Cerebrolysin fully rescues memory and learning capabilities (1a) as well as social behavior (1b) of the injured animals

Such remarkable therapeutic effects in the cognitive domain are highly relevant for TBI patients. It is therefore important to find out if Cerebrolysin's action at the mechanistic level is congruous with these findings. The first question asked by the investigators was: Which are the normal biological and/or pathological processes targeted by Cerebrolysin? Among the key, statistically significant experimental findings were: increased hippocampal neurogenesis, reduced accumulation of amyloid precursor protein (APP) in the injured brain, and the preservation of axonal integrity after trauma. Hippocampal neurogenesis has been linked previously with neurorepair processes responsible for the recovery of memory and learning function after brain injuries. The strong neurogenic effect of Cerebrolysin accounts for or at least closely correlates with the results of the functional test in the Modified Morris Water Maze. After a moderate TBI, the accumulation of APP is considered as a marker of heightened risk for the development of dementia. Indeed, in tested, saline-treated animals, APP accumulation correlated inversely with cognitive recovery. Cerebrolysin treatment prevented TBI-induced accumulation of APP in the relevant brain regions (dentate gyrus, cortex, and CA3). The preservation of axonal integrity is highly correlated with functional recovery after TBI. While seriously compromised in the saline-treated group, this vital structural brain feature was completely recovered in Cerebrolysin treated animals (**Fig. 2**).

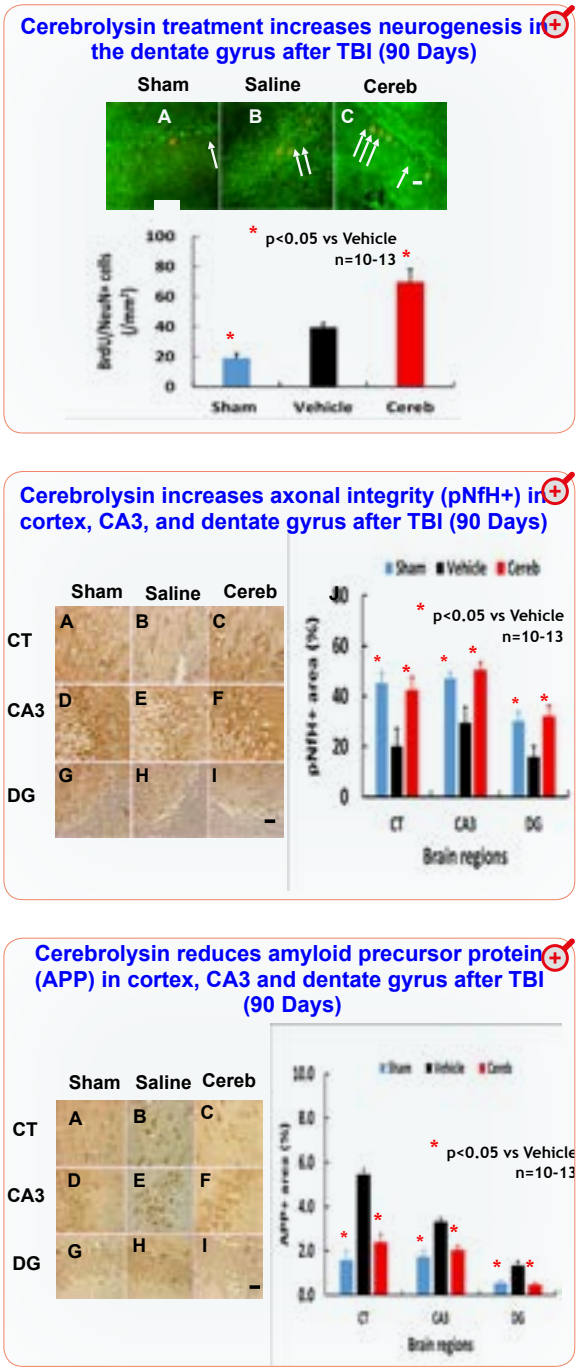


Fig. 2 After TBI, Cerebrolysin increases neurogenesis, promotes axonal integrity and prevents the accumulation of amyloid precursor protein (APP) in the investigated brain regions

Further experiments confirmed a complex, multi-modal mechanism of action of Cerebrolysin. One of the key observations concerned the impact of Cerebrolysin on the integrity and well-being of the cerebral microvasculature. After the brain injury, the vital, complex interaction between the brain vasculature and the parenchymal tissue is compromised. At the physiological level, this is, in fact, the main source of secondary brain injury. One of the key markers associated with vascular malfunctioning is a profound increase in fibrin deposition. This, in turn, leads to an increased inflammatory response within the vascular system. Cerebrolysin was shown to block fibrin deposition. As expected, this prevented the increased production of pro-inflammatory cytokines in the endothelium (**Fig. 3**).

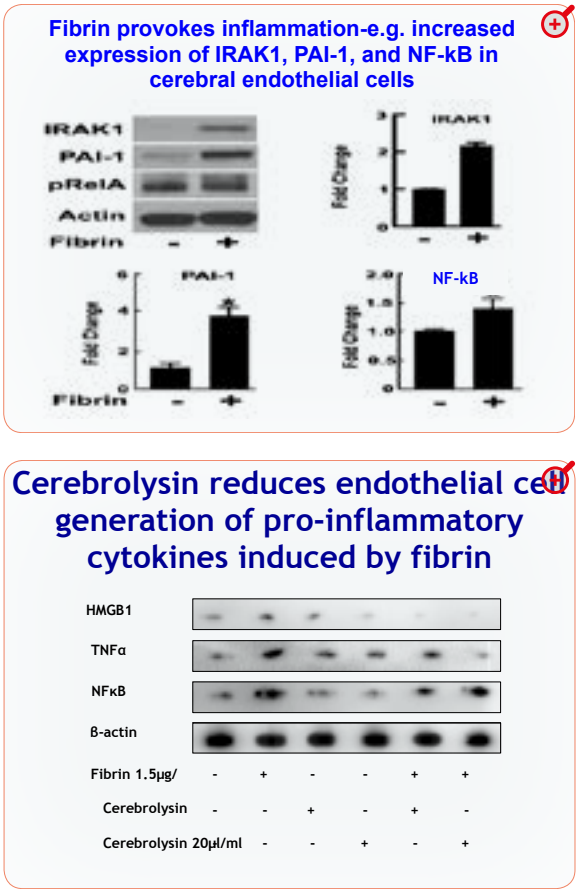


Fig. 3 The injury-related deposition of fibrin, leading to a cascade of pro-inflammatory processes within the brain microvasculature, is ameliorated by Cerebrolysin

Another benefit linked to preventing the fibrin deposition in the microvasculature is decreased blood-brain barrier (BBB) permeability. Dr. Chopp suggested, that all these findings establish Cerebrolysin as a potent vascular therapy. Some of the known contributing factors of this pharmacological pathway are angiopoietin 1 (ANG 1) and vascular endothelial growth factor (VEGF). These key regulatory factors are strongly stimulated by Cerebrolysin in the endothelial cells.

Finally, Dr. Chopp mentioned the ability of Cerebrolysin to induce specific clusters of micro-RNAs (miR 17-92). This process requires stimulation of sonic hedgehog (Shh)-dependent pathway, which was previously reported for Cerebrolysin by the same investigators. miRs are important regulators of various recovery processes. miR 17-92 cluster, which is stimulated by Cerebrolysin, regulates neurological functions, neuronal outgrowth, hippocampal neurogenesis, and processes responsible for anxiety and depression (**Fig. 4**).

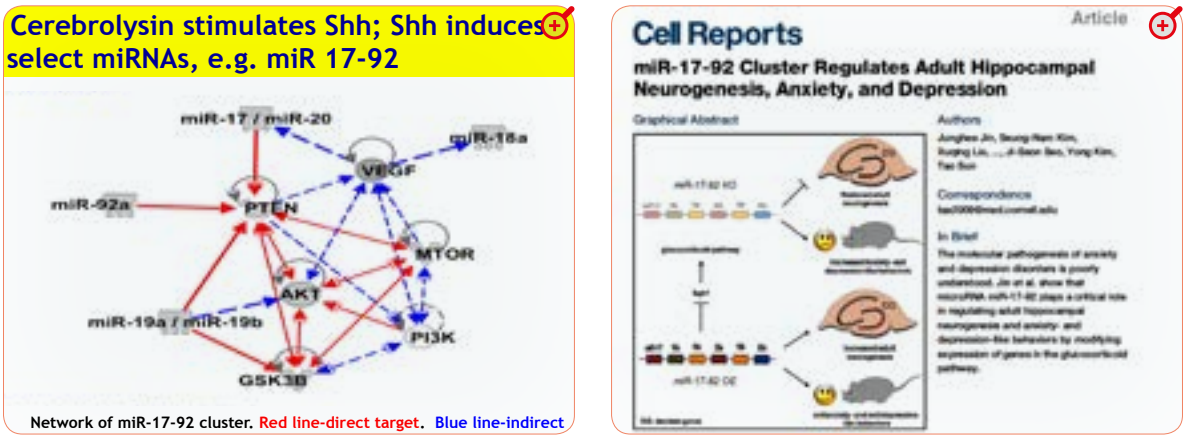


Fig. 4 Cerebrolysin stimulates the miR 17-92 cluster responsible for the regulation of the key recovery-related processes, including the reduction of anxiety and depression

These mechanistic findings are consistent with the observed effects of Cerebrolysin on functional outcome in stroke and TBI models. Cerebrolysin is a multimodal agent that has the basic, underlying, restorative physiological effect after the brain injury. It has also a vascular therapeutic effect, manifesting itself by transforming the pro-inflammatory status of the vasculature into an anti-inflammatory, pro-recovery status. Finally, Cerebrolysin stimulates the important cluster of micro-RNAs (miR 17-92) which are responsible for the regulation of the key molecular pathways underpinning processes of neurorecovery.

Challenges and advances in neurotrauma treatment

Martin Rakusa

Department of Neurology, University Medical Centre Maribor, Maribor, Slovenia

ABSTRACT:

The overall incidence of TBI in Europe is estimated between 198 and 325 people per 100,000 per year, with fatal outcome in 10.5 people per 100,000 per year. These numbers are even higher in low and middle-income countries. Direct and indirect lifetime economic costs of mild, moderate and severe TBI are estimated at 90 billion dollars in the USA. Thus TBI represents an important medical condition with a significant impact on personal and public health.

There is no specific treatment for TBI. Treatment options depend on the severity of the TBI and its symptoms. The results from recent studies suggest several possibilities for better outcome of TBI patients. First, TBI patients should be managed by interdisciplinary teams in specialized centers. Patients with severe TBI in the acute phase may benefit from intracranial pressure monitoring. Several studies have demonstrated the association between ICP monitoring and lower in-patient mortality. Drugs without proven benefit should be avoided throughout all stages of rehabilitation.

A potential treatment strategy may include the use of "neurorecovery" drugs. The results from two meta-analyses have demonstrated a positive effect of Cerebrolysin on the restoration of brain function after TBI. To recognise all major TBI complications, e.g. PTSD, depression, and cognitive deficits, long-term follow-up of patients is needed.

New clinical trials with the multidimensional analysis approach are setting a new gold standard. In the future, we may expect some positive results which will help us to better treat patients with TBI.

For the preparation of his talk, Dr. Rakusa reviewed literature from the last 5 years and found out that for measured evaluation of certain therapies it was necessary to extend the search beyond that period. The goal of the talk was to give a comprehensive picture of the state-of-the-art in TBI management and, accordingly, it covered epidemiology, measures of outcomes and preferred scales, recommended treatments (both pharmacological and non-pharmacological), and plausible steps forward.

TBI is a huge medical and social problem that affects about 70 mio people every year (worldwide). The related costs are enormous, with calculated 90 billion USD per year (direct and indirect costs) in the US alone. The socio-economical burden weighs heavily on families that care for patients. In victims with moderate to severe TBI (45% of all cases), the most common outcome is death. The most prominent outcome measures used in clinical trials are the length of stay in the ICU, followed by 6 months mortality, Glasgow Coma Scale (gauging the severity of TBI), Glasgow Outcome Scale, Glasgow Outcome Scale Extended, and Abbreviated Injury Scale. While dire health consequences of moderate and severe TBI can be clinically defined and measured shortly after the incident, in mild TBI (GCS 15-13) patients the situation is different. After a quick evaluation, such patients are discharged home and there is usually no follow-up until long-term complications surface and prompt specialist consultation. Among them are depression, PTSD (posttraumatic stress disorder), cognitive decline and even dementia. In a large study investigating the prevalence of dementia among American veterans suffering from TBI, the correlation between the severity of the trauma and onset of dementia was established (**Fig. 1a**). Even mild TBI more than doubled the incidence of dementia among the victims.

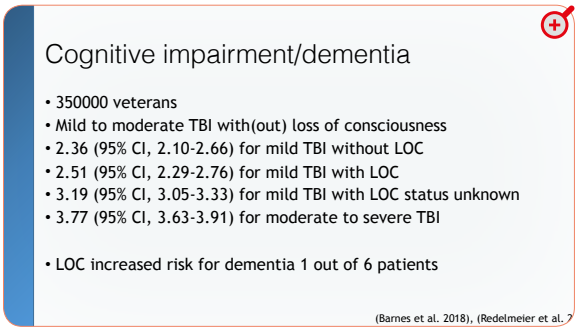


Fig. 1a

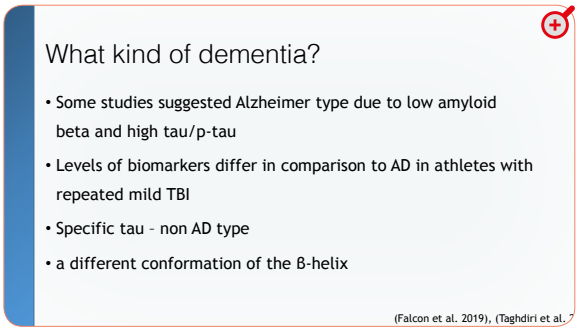


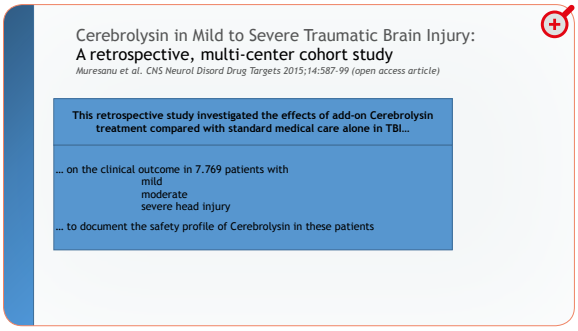
Fig. 1b

The causal relationship between TBI and dementia denotes a major medical challenge that must be addressed with novel treatment approachess

Interestingly, loss of consciousness (LOC) was found to be an independent predictor of cognitive impairment/dementia in this study. Dr. Rakusa commented that recent studies have found differences between patients suffering from Alzheimer's disease and those suffering from dementia after repeated mild TBI (e.g. athletes). The molecular markers appear to diverge between these populations suggesting clinically distinct entities (**Fig. 1b**).

One of the most important types of non-pharmacological interventions in TBI is the intracranial pressure (ICP) monitoring. Increased ICP can cause the secondary injuries and current clinical guidelines support Level II b recommendation for this approach. The choice between 20% mannitol and 3% hypertonic saline appears to be arbitrary, as shown by recent clinical investigations. On the other side, the craniectomy was evaluated as an alternative to the medical approach (RESCUEicp trial). Depending on the definition of a "good outcome" one can appreciate lower mortality in patients who underwent craniectomy but might also criticize the increased rates of vegetative state. Hypothermia was investigated in a population of 387 patients (Andrews et al., 2015), but no clinical benefits were reported (as measured with GOSE). At the same time, hypothermia was shown to benefit patients with severe TBI (AIS 3-4) when used as a means of fever control.

Dr. Rakusa divided the pharmacological interventions into three groups: with no effect, with mixed effect, and with possible effect. The first category encompasses drugs like glibenclamide, cyclosporin-A, and anticonvulsants (phenytoin/levetiracetam). Although anticonvulsants do not exert any neuroprotective action, they are still needed and used for their primary intended purpose. The substances with mixed effect - progesterone and erythropoietin - were evaluated in the clinical trials which, individually, did not confirm any clinical benefit. However, in the case of erythropoietin, the meta-analysis of five clinical trials found a non-linear correlation between the dose and the positive outcome. It also revealed a lower 6-months mortality. The category of interventions with possible therapeutic effects enlists agents that await further clinical evaluation. Among them are nitric oxide (NO)-synthase inhibitor (VAS203), statins, N-acetyl-L-cysteine and Cerebrolysin. Dr. Rakusa mentioned a large retrospective, multicenter cohort study (n=7769), investigating Cerebrolysin treatment in mild to severe TBI patients (**Fig. 2**).



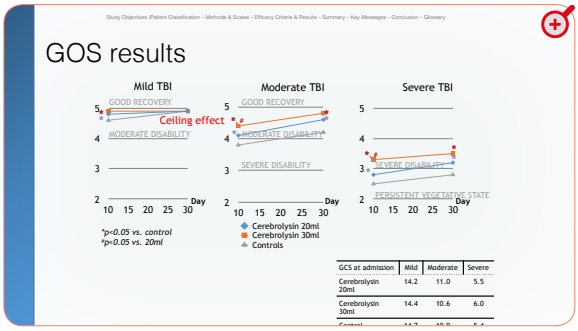


Fig. 2 Treatment of TBI patients with a neurotrophic agent, Cerebrolysin, suggests benefits for more severely affected patients

The therapeutic effect of Cerebrolysin was dose-dependent but could be detected only in patients with moderate to severe trauma (probably due to the treatment ceiling effect in mild TBI cases). These findings are in agreement with earlier studies, results of which are reflected in the Canadian ERABI-Group (Evidence-based Review Acquired Brain Injury) guidelines that incorporated Cerebrolysin with the following wording: "Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy".

The predicament of TBI requires new approaches on all levels. Concluding his talk, Dr. Rakusa stressed a need for multidisciplinary management of TBI patients. In such a complex therapeutic context, it is important to avoid pharmaceuticals that could bring more damage than benefits. Concerning the clinical trials, the long-term follow-up must be included with a special focus on depression, PTSD and dementia. The trials should be appropriately designed, including more sensitive scales (e.g. QOLIBRI - Quality of Life After Brain Injury) and multifactorial statistics. Ongoing education of neurologists is also required to improve the clinical management of TBI patients. A recent study conducted by Dr. Rakusa (2014) indicated that this knowledge is currently inadequate.

New vistas in TBI research – Results from CAPTAIN studies and the multidimensional methodology

Johannes Vester

Department of Biometry and Clinical Research
IDV Data Analysis and Study Planning, Krailling, Germany

ABSTRACT:

An evaluation of the neuroprotection intervention studies conducted over the last 30 years has indicated that a limited understanding of the underlying biological concepts and methodological design flaws are the major reasons for the failure of pharmacological agents to demonstrate efficacy. Cerebrolysin is a parenterally-administered neuropeptide preparation that acts in a manner similar to endogenous neurotrophic factors. Cerebrolysin has a favorable adverse effect profile, and several meta-analyses have suggested that Cerebrolysin is beneficial as dementia and stroke treatment.

CAPTAIN is a randomized, double-blind, placebo-controlled series of trials to investigate the effects of Cerebrolysin on neuroprotection and neurorecovery after TBI using a multidimensional ensemble of outcome scales. The CAPTAIN I and CAPTAIN II trials are the first TBI trials with a 'true' multidimensional approach based on full outcome scales while avoiding prior weaknesses, such as loss of information through "dichotomization," or unrealistic assumptions such as "normal distribution."

Results reveal a high assay sensitivity of the chosen approach, suggesting beneficial effects of Cerebrolysin on outcome after TBI. A formal meta-analysis of the two trials is confirming the beneficial effects in fixed effects as well as in random effects models (P<0.05, I-squared 0%).

The progression of clinical research in TBI during the last few decades has led recently to major methodological upheaval. How and why this shift happened, and what are its consequences for the field, was the topic of Dr. Vester's talk.

In 2010, the Europe-based IMPACT group issued recommendations for improving the design and analysis of clinical trials in moderate to severe traumatic brain injury (Maas et al., 2010). The reason for this revision was the critical review of the efforts of the last 30 years. During this period, clinical trials with the traditional design were unable to confer statistically significant results in neuroprotection. As a result, all studied neuroprotective agents were denied approval in Europe and the US. The question arose: Do we have the right tools to detect the treatment effects in TBI patients? A classical recombinant clinical trial (RCT) in neurosciences employed a single outcome measure. In the case of TBI, it was usually the Glasgow Outcome Scale (GOS). Importantly, the proportion of patients with favorable outcome had been evaluated using the dichotomization principle (after dividing the scale into two parts). For example, the safety and tolerability of cyclosporin A in severe TBI patients (Mazzeo et al., 2009) was investigated in this way. The results were categorized as the "bad outcome" defined as dead, vegetative or with severe disability, and the "good outcome" defined as a moderate disability or good recovery. Similarly, the ProTECT III trial (investigating progesterone for TBI) used dichotomization of the GOSE scale. Such binary thinking inevitably excluded the majority of patients from the statistical analysis and, in effect, drastically reduced our ability to detect statistically significant treatment effects in these trials (**Fig. 1**).

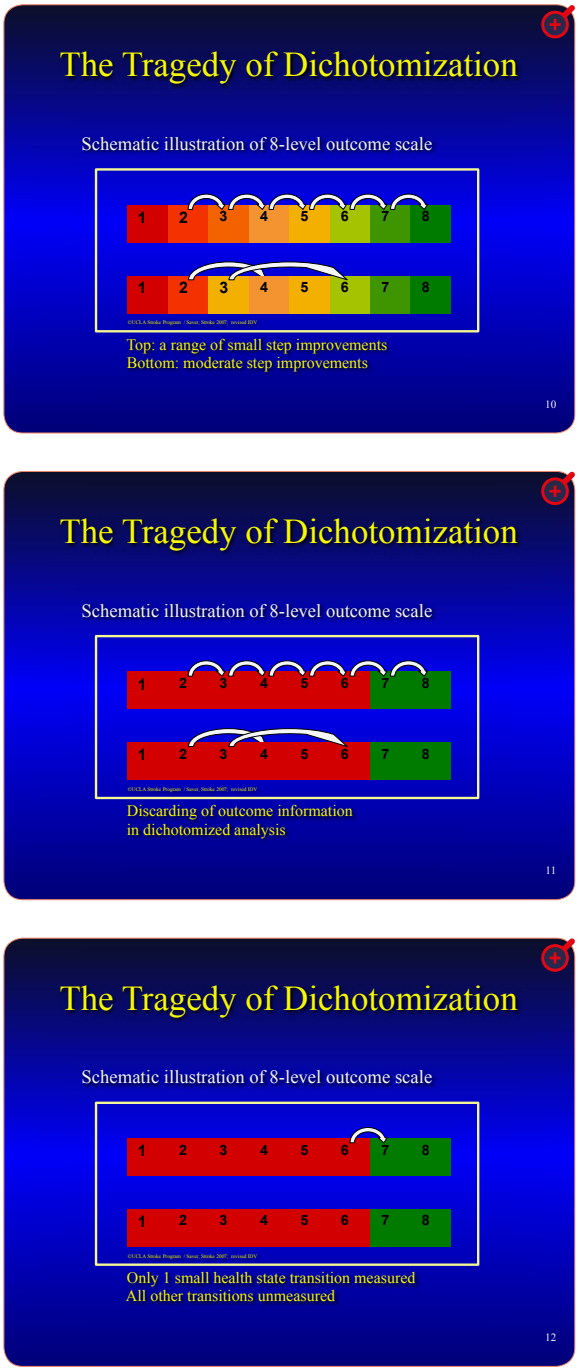
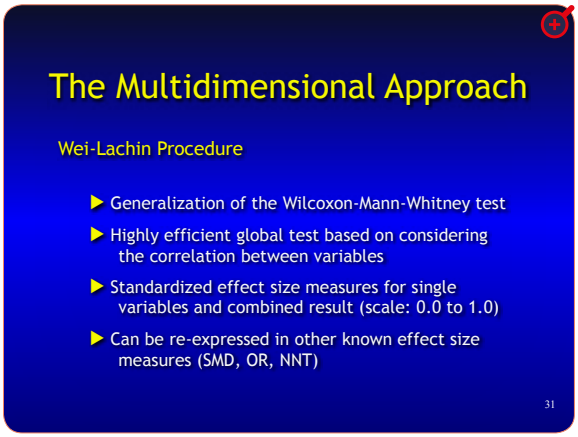


Fig. 1 The illustration of the mechanism through which dichotomization of outcome limits our ability to identify potentially beneficial treatment effects

Dr. Vester illustrated the deceiving (and unscientific) nature of dichotomization using the example of the ECASS II trial investigating the rtPA treatment in stroke (Hacke et al., 1998). When the investigators chose 0-1 on the mRS scale as a positive outcome cutoff point, the results of the trial were neutral (P = 0.277). However, when another group of researchers chose 0-2 mRS instead, in the posthoc analysis, the results changed into significantly positive (P = 0.024). The same patients, the same trial and the same outcome measure (mRS) led to conflicting statistical results and to opposing conclusions about the clinical utility of the treatment. This happened, due to an arbitrary choice of the cutoff point for dichotomization on the mRS scale. The first important lesson had been learned: we should use the full outcome scales, instead of the dichotomized scales.

Another critical issue identified in the past trials was the choice of the outcome scale. This choice, again, appeared to be mostly made arbitrarily. Typically, one would choose the Glasgow Outcome Scale, or consider one of the more specific measures related to cognitive function, motor function, anxiety/depression or health-related quality of life (HRQoL). The solution proposed by the IMPACT group went against this common approach. Instead, they submitted that: "Outcome after TBI is by definition multidimensional including neuro-physical disabilities and disturbances in mental functioning" (Maas et al., 2010). This view was supported by the US Traumatic Brain Injury Clinical Trials Network, which stated: "Multiple measures are necessary to address the breadth of potential deficits and recovery following TBI" (Bagiella et al., 2010). The notion that single functional assessment scales are not adequate for identification of important deficits after TBI was also formulated by S. Margulies and the Traumatic Brain Injury Workshop Leaders (Combination Therapies for Traumatic Brain Injury: Prospective Recommendations, 2009). The multidimensional strategy to capture the complexity and true clinical picture of recovery from TBI was finally adopted as a new standard in clinical research. This strategy materialized for the first time in the citicoline trial (COBRIT, 2009). The investigators used 9 different outcome measures developed in the US. However, due to the lack of reliable alternative statistical methodology at that time, they continued to use the dichotomization of the chosen outcome scales. The results were handled through the multidimensional analysis, but only after dichotomization. This situation was subsequently rectified by The International Biometric Society which introduced powerful and robust multiple endpoints analysis (Wei-Lachin procedure, **Fig. 2**).



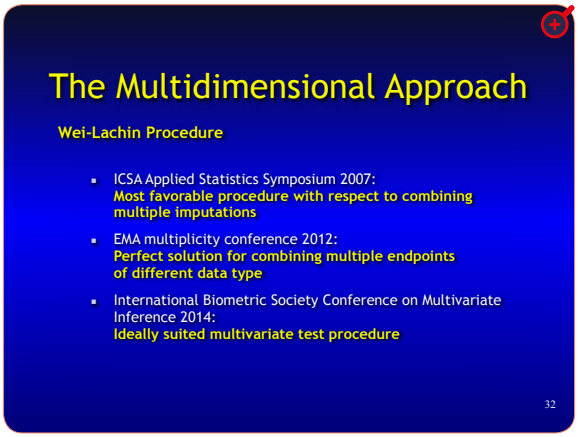


Fig. 2 The Wei-Lachin procedure – a modern multidimensional statistical approach to assess the global status of a patient in a clinical trial

This methodology was accepted by the European Medicines Agency (EMA) in 2014, which stated: "In clinical trials when a single outcome is not sufficient to describe the underlying concept of interest, it may be necessary to compare treatment groups on multiple correlated outcomes". Interestingly, the Wei-Lachin procedure was already used in 2000 for the approval of Novantrone in multiple sclerosis by the FDA. However, at this point, it wasn't considered a sanctioned standard in clinical research.

In a new approach, we are looking for different outcome measures to define the global status of a patient. In this procedure, the variability of used scales (e.g. motor function, anxiety, depression, processing speed, GOS, etc) powers a composite global score. This approach circumvents the issue of correlation sensitivity between scales, which lowers the statistical power of the analysis. The development of optimal composite scores for different diseases is currently undertaken by various groups worldwide. Additional advantages of the new methodology concern the reduction of the overall cost of the research. In comparison to dichotomization, the full-scale analysis requires on average 36% fewer patients to reach the same statistical power. The single scale outcome requires 60% more patients than a multidimensional test of five outcomes with an average correlation of 0.5. For example, if used for the progesterone ProTECT III trial, a multidimensional approach with 5 outcome scales would have required 335 patients instead of 882 patients. The very first practical application of both principles - multidimensional approach coupled with using full scales instead of dichotomization - for the clinical research in TBI is the CAPTAIN trial series. Dr. Vester presented, for the first time, the results of the two CAPTAIN trials in moderate to severe TBI. In the CAPTAIN I, conducted in Asia-Pacific, the Baseline Prognostic Risk Score (BPRS) was chosen instead of Glasgow Coma Scale for assuring the optimal inclusion strategy. The BPRS is preferable to GCS as it is a first validated prognostic scale with factors recommended by the IMPACT group. It includes a more complete set of seven predictors of outcome: age, motor score, CT, pupillary reactivity, hypoxia, hypotension, and traumatic subarachnoid hemorrhage. The number of patients included was 40 (19 Cerebrolysin and 21 Placebo) and even though this was a small study, the results showed interesting statistical trends (**Fig. 3**).

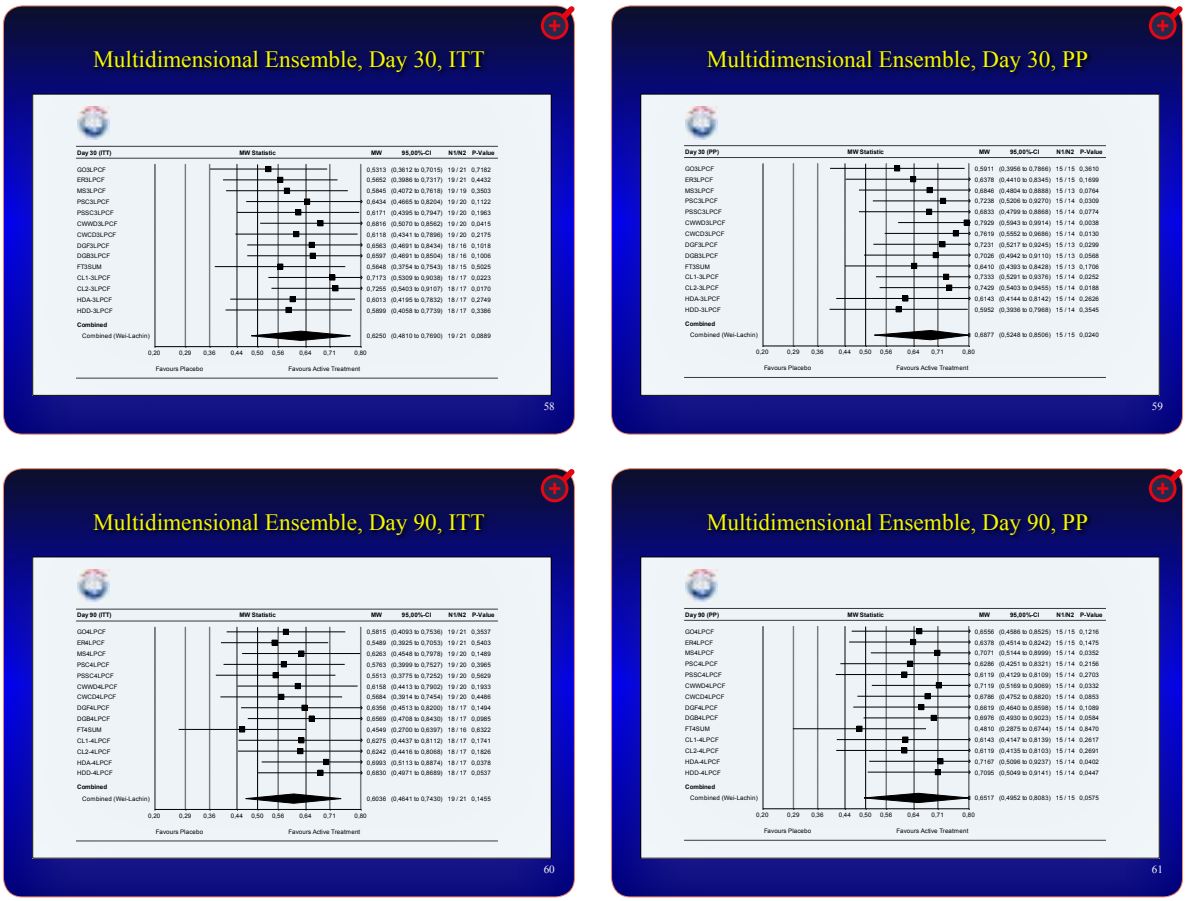


Fig. 3 The multidimensional outcome scales ensemble of CAPTAIN I trial investigating the efficacy of Cerebrolysin in TBI patients

This is a genuine example of statistical power advantage offered by the new methodology, through which one can gather much more clinically relevant data than from the classical approach. For example, it was possible to compare the results of GOS with the progress in processing speed or with the anxiety and depression at days 30 and 90. While the classical GOS score did not move significantly in favor of the treated group, the more specific neurological scales (e.g. depression and anxiety scores) were far more sensitive to the investigated treatment protocol, especially in the context of elapsing time (comparison of day 30 with day 90 results). This is an impressive result when we consider the strong impact of Cerebrolysin on social behavior and anxiety seen in the animal TBI models (see Dr. Chopp's presentation). Moreover, the combined Wei-Lachin index trended strongly toward statistical significance for Cerebrolysin in the ITT population.

The CAPTAIN II trial, conducted in Romania on a larger population (n = 139; Cerebrolysin = 80 and Placebo = 59), employed very similar inclusion criteria and baseline comparability. The primary outcome criteria were pinned at day 90 and featured an identical multidimensional battery of outcome scales. The results confirmed a significant impact of Cerebrolysin on depression and gave a fair clinical picture of the TBI recovery (**Fig. 4**).

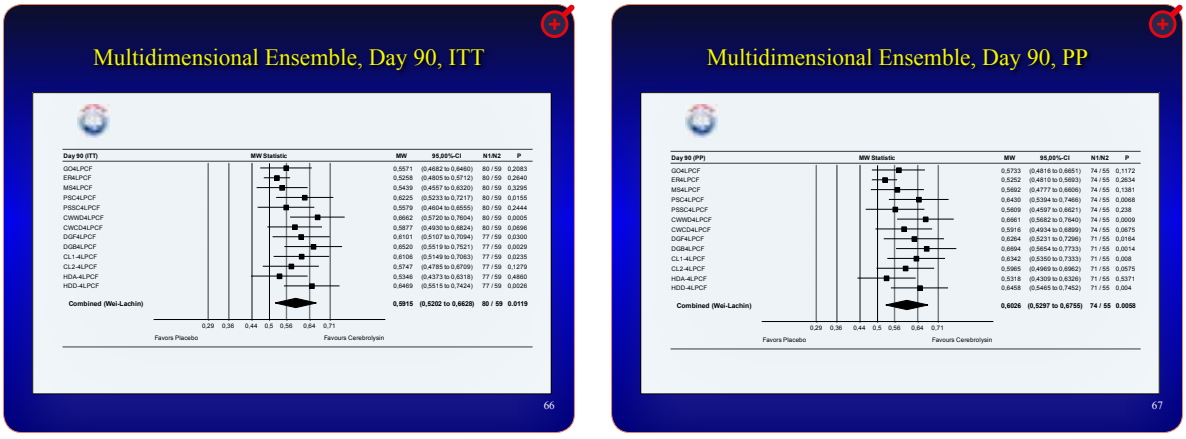


Fig. 4 The results of the CAPTAIN II trial confirmed the overall and anti-depressive action of Cerebrolysin in moderate to severe TBI patients

The meta-analysis of both trials confirmed the consistent positive effects of Cerebrolysin in the moderate to severe TBI patients and illustrated the analytical power and high resolution of the new multidimensional approach in clinical research.

Concluding his talk, Dr. Vester submitted that it is time to re-consider the classical "one-dimensional" or "binary" thinking in clinical research. The multidimensional analysis of full scales opens new opportunities for trials in neurosciences and, accordingly, increases our chances for the development of new, meaningful treatment protocols. The new methodology is perhaps reflecting much closer complex reality of neurorehabilitation than the previous, "one-criterion/one-scale paradigm".

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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