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Advances in the clinical treatment of TBI and stroke

Official Symposium of the
26th International Mondsee Medical Meeting
13th September, 2019 | Salzburg, Austria

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Program of the symposium

Advances in the clinical treatment of TBI and stroke

Welcome speech

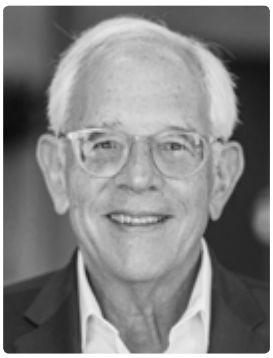
Peter Lackner

Department of Neurology, Otto-Wagner-Spital, Vienna, Austria

On behalf of the Austrian Society for Neurological and Neurosurgical Critical Care and the Austrian Society for Neurorehabilitation, Dr. Lackner greeted the audience of the 26th International Mondsee Medical Meeting taking place in the historic city of Salzburg. He outlined the scientific program of the meeting which was divided into three sessions covering topics of traumatic brain injury, neurocritical care, stroke, and neurorehabilitation. The scientific program was supplemented with clinical case reports strengthening the meeting's lead focus on new neuroprotective and neurorestorative strategies and their potential place in the clinical practice. Dr. Lackner thanked also the founding sponsor of the meeting, EVER Pharma GmbH, for continuously supporting the exchange of expertise in the field of neurology.

Keynote Presentation (introduction by Michael Brainin)

Treatment of traumatic brain injury with Cerebrolysin enhances neurological and cognitive recovery



Michael Chopp

Henry Ford Health System, Detroit, USA

ABSTRACT:

We have previously demonstrated that treatment of penetrating severe traumatic brain injury (TBI) as well as mild closed head injury in rats with Cerebrolysin provides highly significant protective and neurorestorative therapeutic benefits. Here I describe our recent work on the treatment of moderate closed head injury in which Cerebrolysin is initially administered 4 hours post-TBI evoking highly significant therapeutic benefits particularly in learning, memory, emotional and social interaction outcomes.

The data also demonstrate a very robust and a highly significant correlation between these outcomes and biological parameters such as axonal integrity, amyloid protein, neurovascular plasticity and neural damage, demonstrating that the improvement in biological parameters fostered by Cerebrolysin drives neurological and functional improvement.

Mechanisms underlying these therapeutic benefits are described.

We show for the first time that Cerebrolysin directly acts as vascular therapy, augmenting the integrity and function of cerebral endothelial cells and greatly reducing TBI induced vascular inflammatory response. In addition, we demonstrate the multifactorial character of Cerebrolysin by its induction of vascular expression of highly restorative and protective molecules such as Angiopoietin 1 and the morphogen and transcription factor Sonic Hedgehog (Shh).

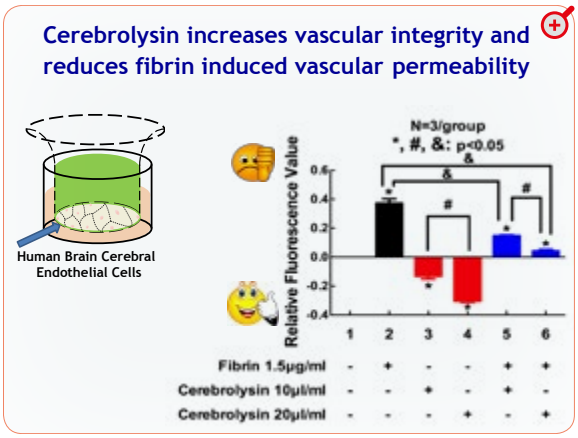
We then demonstrate that Shh upregulated sets of highly restorative microRNAs, short non-coding post-transcriptional regulators of gene expression. Among the miRs upregulated by Shh is the family miR-17-92, which greatly promotes axonal outgrowth and substantially reduces anxiety and depression in rodent models.

In summary, we provide new data detailing the therapeutic benefits of Cerebrolysin and provide fundamental and novel insight into its mechanisms of action.

According to the most recent epidemiological data, even a mild TBI can have serious long-term health consequences. Yet, people engage daily in activities (including sports) resulting in repetitive brain injuries. There is a need for new effective treatments and Dr. Chopp's team is strongly engaged in this field. One of the areas of their research concerns the use of neurorestorative strategies employing Cerebrolysin in brain injury models.

Using the well-established experimental rat model of closed TBI (Marmarou et al., 1994), the researchers investigated Cerebrolysin treatment initiated 4h post-injury and lasting for 10 days. For assessment of behavioral changes, they used the modified Morris Water Maze test which gauges the spatial orientation, learning, and memory of the rats. These vital cognitive features were strongly inhibited due to TBI and Cerebrolysin recovered them completely (day 90). The treated animals showed no cognitive deficits and behaved identically to the healthy controls. Comparably significant results came from the experiments assessing the impact of TBI on social behavior. The onset of depression and a sharp decline in exploratory behavior are common in both TBI patients and experimental animals. At the same time, the quality of life (recovery) after brain injury is strongly impacted by social interactions. The Three-Chamber Test employed by the investigators helps in the assessment of this domain. As expected, after TBI, the animals exhibited depressed social interactions manifesting themselves in losing interest in novelty exploration (time spent on socializing with other animals). The treatment with Cerebrolysin fully recovered all elements and qualities associated with the social behavior of healthy control animals. The investigators postulated that the pharmacological effects of Cerebrolysin should be reflected in its impact on the processes of brain plasticity. The axonal integrity and density, measured in the functionally relevant brain areas (dentate gyrus, CA3, and cortex), is a reliable experimental plasticity assessment tool. This vital structural feature was severely compromised in the employed TBI model. After treatment with Cerebrolysin, a profound increase in the axonal density was evident. The histological picture was no different than in healthy control animals. Another important factor linked to the functional outcome after TBI is the accumulation of amyloid precursor protein (APP). APP deposits correlate with the decline in cognitive function and are used as a marker in experimental models. In contrast to injured untreated rats (control), Cerebrolysin prevented the accumulation of APP in the brain of treated animals, as measured 90 days post-TBI. These experiments shed a light on the impact of Cerebrolysin on important biological processes underlying recovery from brain injury.

To better understand the mechanisms through which Cerebrolysin modulates these processes, the investigators looked into one of the fundamental sources of the secondary brain injury – the inflammation within the microvasculature. It is deemed responsible for ongoing parenchymal tissue damage, long-term functional deficits, and cognitive decline. One of the hallmarks of the malfunctioning microvasculature is the fibrin deposition. It triggers the increased production of the pro-inflammatory cytokines by the endothelial cells. The ensuing leakage of the blood-brain barrier (BBB) leads to ongoing structural and functional damage. Cerebrolysin acts as a potent vascular therapy. It inhibits the deposition of the fibrin in the microvasculature, decreases the production of pro-inflammatory cytokines (blocks the inflammatory processes) and protects the integrity of BBB (**Fig. 1**).



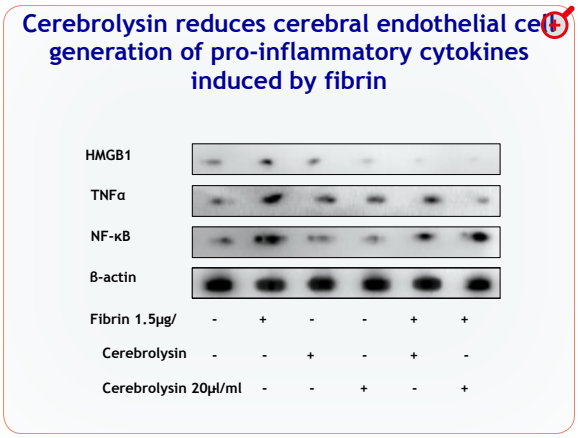
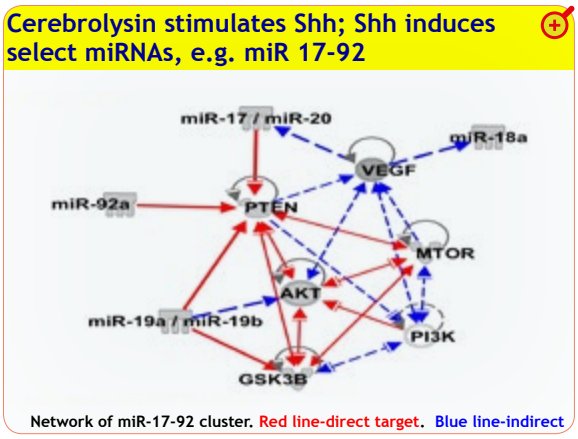


Fig. 1. The potent anti-inflammatory properties of Cerebrolysin establish it as an effective neurovascular therapy

Additionally, Cerebrolysin was shown to stimulate the production of vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang 1), key molecules involved in maintaining the functions of BBB. Another regulatory route ascribed to Cerebrolysin by Dr. Chopp's research involves the stimulation of micro-RNAs (miR17-92 cluster).

These small regulatory molecules are responsible for the concerted deployment and control of the endogenous neurorecovery processes. It was shown that miR17-92 cluster increases axonal density and regulates complex emotional features like anxiety and depression (**Fig. 2**).



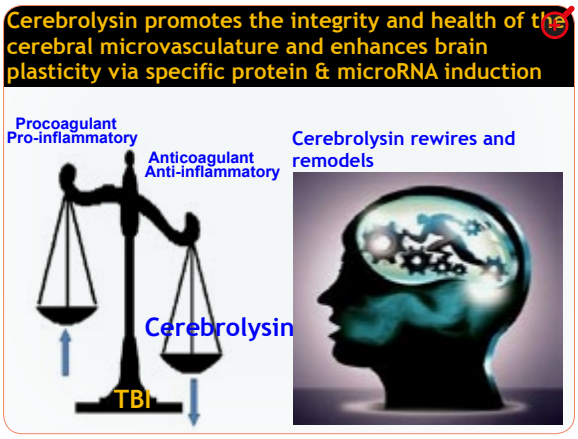


Fig. 2. The regulatory pathways linked with Cerebrolysin-mediated therapeutic effects

The new unpublished data from Dr. Chopp's laboratory showed that miRs produced in platelets derived from the blood of the TBI/stroke-injured animals promote leakage of BBB. The pro-inflammatory cascade leading to secondary brain injuries appears to be driven by multiple vascular events.

Cerebrolysin treatment promotes the opposite effects – a shift toward anti-inflammatory, pro-recovery processes within the microvasculature. This action prevents or at least limits the extent of the secondary brain injury and facilitates the recovery of lost functions.

Outcomes predictions in TBI – determinants and future perspectives

Peter Lackner

Department of Neurology, Otto-Wagner-Spital, Vienna, Austria

ABSTRACT:

Due to the complexity of traumatic brain injury (TBI), outcome prediction for individual patients is a big challenge. After the trauma, many factors are influencing the further course of the disease. Hence not only the initial clinical presentation, secondary brain injury or systemic complications during the acute phase of TBI, but also timing and intensity of neurorehabilitation are known determinants of outcome. A better knowledge of the processes is crucial for the development of new treatment strategies and management concepts.

However, due to patient heterogeneity, large cohorts are needed to identify the solid outcome predictors. The International Initiative for Traumatic Brain Injury Research supports the further development of common data elements for TBI as a method for international comparative effectiveness research (CER). First CER data from large international studies are available giving us a new view on determinants for an outcome prediction in TBI patients.

In addition, studies on promising pathophysiological, diagnostic and therapeutic concepts will be presented and future perspectives will be discussed.

The currently acknowledged and some novel ideas on outcome prediction in TBI patients were collected by Dr. Lackner and presented in his comprehensive lecture. Most of the clinical data about outcome predictors come from population studies. When applying them to the individual patient one has to keep in mind that all prognostic factors could be a false positive or false negative. The early recovery after severe TBI presents a particular challenge as it is very difficult to correctly interpret and control all the likely confounders and manage all the potential complications. The ethical question on the definition of favorable outcome must be clarified within the given medical and social environment of a patient. For example, the determination of the permanent vegetative state in young TBI patients with a prolonged coma is very difficult to make, as it results in the choice between applying the rehabilitation program or discharge to a nursing facility. In the case of TBI, every patient is different and the clinical picture is always specific for any given patient. This heterogeneity deepens further due to the plethora of secondary brain injuries which always follow the primary injury (**Fig. 1**).

In looking for the outcome predictors, increasing the sample size of the study population can be a helpful method as represented by the IMPACT study effort (Mass et al., 2008). Over 9 000 patients were included in this registry and such outcome predictors as motor score, pupillary reactivity, computed tomography (CT) imaging and subarachnoid hemorrhage (SAH) were tagged. Delayed cerebral ischemia normally associated with aneurysmal SAH is rarely observed in TBI patients. Dr. Lackner mentioned the novel concept explaining the relationship between SAH and TBI outcome – the glymphatic system. The idea was introduced by the Maiken Nedergaard group (**Fig. 2**) which found out that the flux of cerebrospinal and interstitial fluids is regulated by a pressure gradient between venal and arterial systems of the brain.

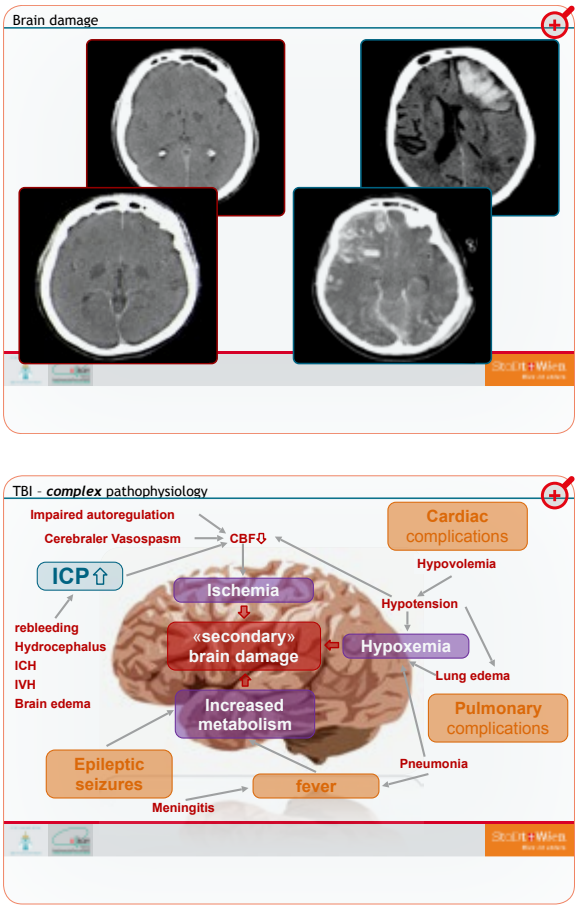


Fig. 1. The complex, heterogenous pathophysiological picture of TBI makes the prediction of the outcome uniquely difficult

This system is highly active during sleep and serves to dispose of the toxic brain metabolites. The blocking of perivascular spaces, e.g. due to SAH, causes impaired clearance of the waste products and suggests the relevance of SAH as an outcome predictor after the TBI.

Among the advanced neuroimaging techniques, the MRI is considered superior to CT. It allows detecting the diffuse axonal injury as well as the fiber tracking (diffusion tensor imaging, DTI) which closely correlates with the clinical status of a patient. Therefore, MRI can be used as an objective verification measure in the clinical process. Somatosensory evoked potentials (SSEP; bilaterally absent SSEP in the prognosis of permanent vegetative state or death) and EEG (early increased reactivity correlates with the good outcome) are electrophysiological methods of value in predicting outcome after TBI. The multimodal neuromonitoring is in its early phase of development, but Dr. Lackner's own experience indicates that it can already enhance patient guidance.

As seen in the neurorehabilitation practice and the literature, the timing and the intensity of neurorehabilitation is an outcome determinant after TBI. Generally, and if possible, the earlier it starts and the more intense it is, the better is the functional outcome.

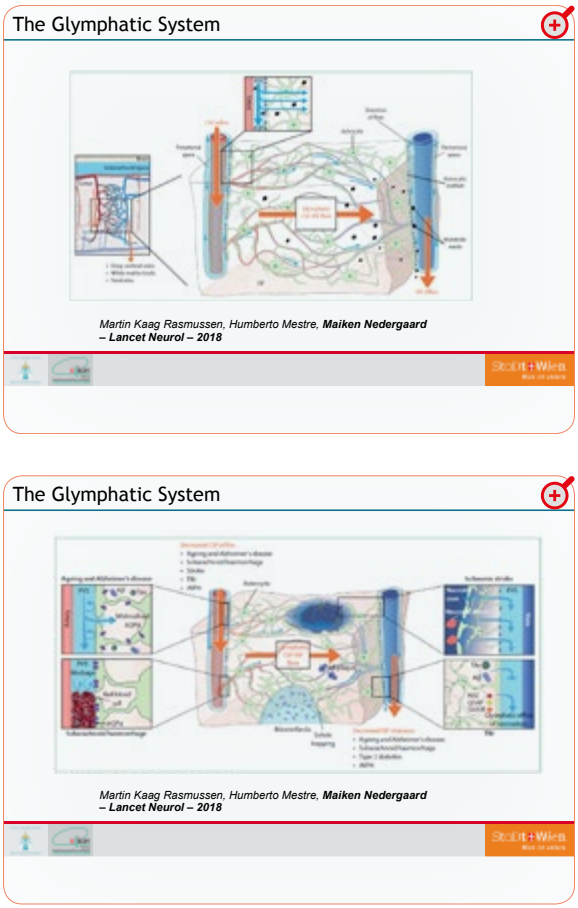


Fig. 2. The glymphatic system concept links secondary brain injuries with the failure to dispose of the toxic metabolites

Finally, Dr. Lackner discussed the integrated TBI treatment approach. He underlined the importance of establishing continuous treatment pathways throughout all phases of TBI care. Optimally, TBI management should include pre-hospital phase, hospital phase (the acute treatment), inpatient rehabilitation, and neurorehabilitation in an outpatient setting. Particularly, the last phase requires more attention and structure as it is inadequately developed and executed.

CENTER-TBI: Mapping the contemporary landscape of TBI in Europe

Andrew Maas

Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium

ABSTRACT:

Traumatic Brain Injury (TBI) is a field in medicine with huge unmet needs. In Europe, over 2 million people are admitted to hospitals annually with a diagnosis of TBI, of whom more than 80.000 die.

The CENTER-TBI project (Collaborative European NeuroTrauma Effectiveness Research: www.center-tbi.eu) is a large-scale observational European study, conducted in 65 centers from 19 countries in Europe and Israel that addresses all severities of TBI. It aims to advance the care for TBI by developing precision medicine approaches and by identifying best practices through comparative effectiveness research. Patients are stratified upon enrollment by care pathways into the ER (Emergency room), admission and ICU strata.

Recruitment was completed in December 2017 with a total enrolment of 4559 patients in the Core study and 22,849 in the Registry. In the Registry, 81% of patients were enrolled in the ER and Admission strata, and over 95% of these had sustained a mild TBI – which therefore represents the most common form of TBI. The Core study showed that 53% of patients in the Admission stratum and 30 % of those in the ER stratum had not attained a full good recovery at 6 months after injury.

Overall, the median age was nearly 50 years, double that of previous observational studies, and 28% of patients were over 65 years of age. Falls are now the most common cause of TBI, especially in the elderly. In addition, CENTER-TBI has created large neuro-imaging and blood/serum repositories.

Detailed results will be presented.

Dr. Mass began his lecture where Dr. Lackner concluded his – with a note about the importance of the continuity of care across all TBI severities. If the pre-hospital care is inadequate, the secondary brain injuries can be so devastating that the battle for a patient is lost. This would happen irrespective of the quality of the hospital care provided downstream. Likewise, if a patient gets outstanding care in the hospital, but this benefit is not consolidated by good post-acute care, the patient will lose that benefit. Remembering the significance of the continuity of TBI care is the most important message of my lecture, stated Dr. Maas.

The main topic of the lecture was the large scale observational study – CENTER-TBI – encompassing 44 scientific institutes, 65 sites of data collection, 19 countries (joined later by Australia, China, and India) and 223 group contributors. This project started in October 2013 and falls under the umbrella of InTBIR, the international initiative for brain injury research, launched by the European Commission, NIH and Canadian Institute for Health Research. The essential components of CENTER-TBI include healthcare provider profiling of the participating sites, evidence generation (core data study, N=5400; registry, N=20-25000), Neuro-Imaging Repository and BioBank, optimizing existing evidence through Living Systematic Reviews (LSR), and knowledge transfer (**Fig. 1**).

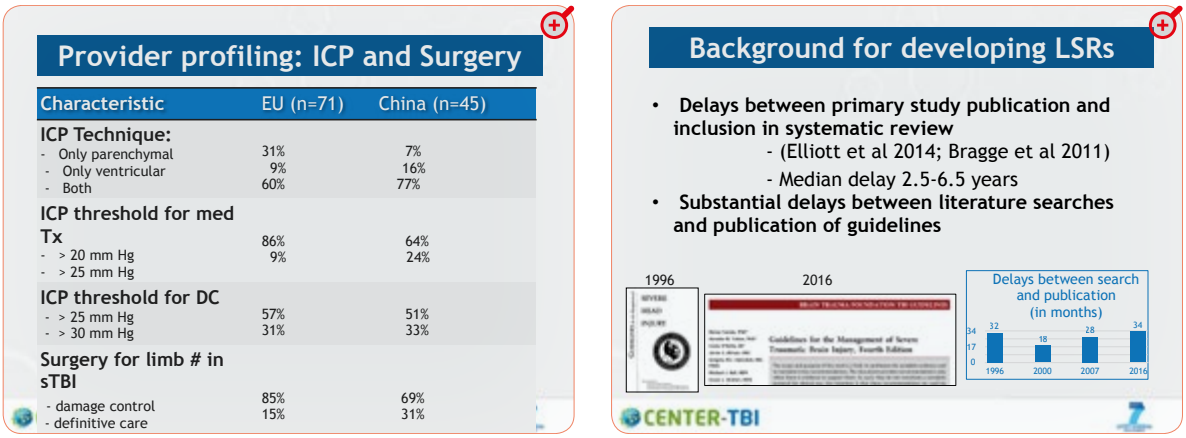


Fig. 1. CENTER-TBI care provider profiling and living systematic reviews help in correlating variation in the clinical practice with the most relevant and current clinical research data

The recent overview of the evolution of evidence and recommendations for the medical management of TBI (Volovici et al., 2019) indicates that the guidelines changed substantially over the past 20 years, with 70% of former recommendations either discarded or downgraded. This occurred mainly due to increasing methodological rigor in grading the existing evidence. There is a need for improved quality evidence that informs and considers clinical practice. On the other hand, there is a need for improved characterization and classification of TBI for precision diagnosis using multimodal approaches. In this context, the heterogeneity of existing practices can be used to our advantage in conducting comparative effectiveness research and in the identification of the best practice. These are the main goals of the CENTER-TBI. The project uniquely challenges the current classification of mild, moderate and severe TBI, by replacing it with differentiating patients according to their care pathway (**Fig. 2**).

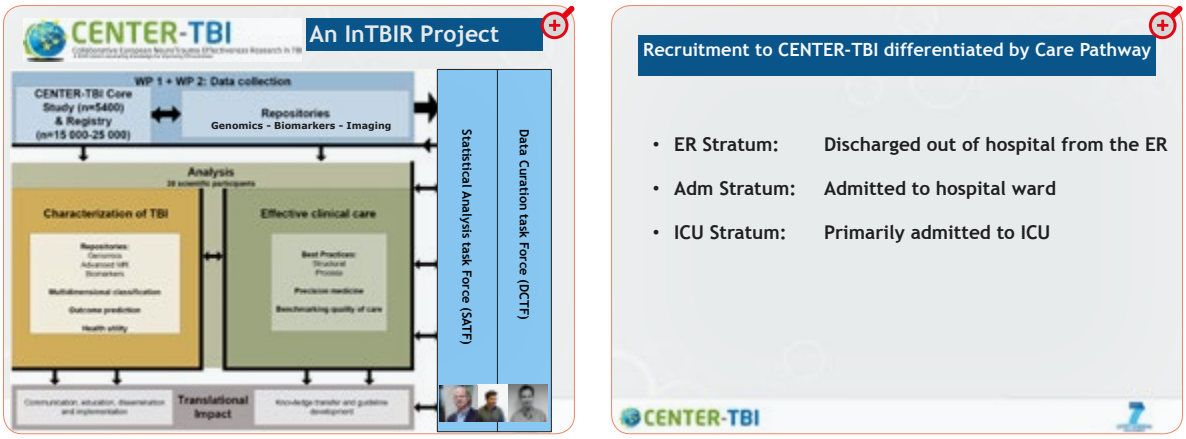
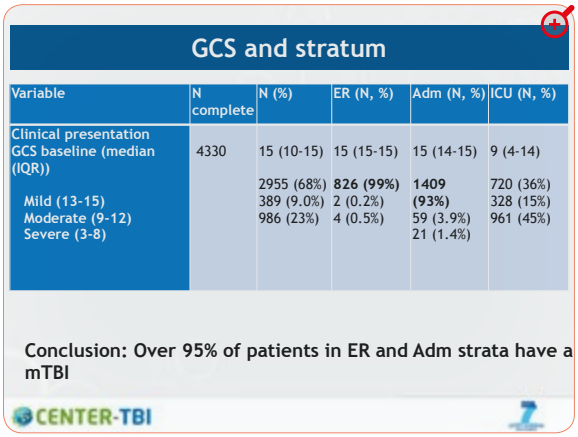


Fig. 2. The focus of CENTER-TBI is on evidence for informing the best clinical practice and precision diagnosis while distinguishing patients by their care pathway

Dr. Mass went on to present the first results (the descriptive analysis) of the CENTER-TBI project that have been published during this meeting (in Lancet Neurology). A quarter of the patients in the ICU stratum were secondarily referred. While overall, the time from the injury to the hospital is around 1 hour for patients arriving directly, the secondarily referred group is admitted within 5 hours. We do not yet know if such a delay translates into the differences in the outcome, but we know that the proportion of secondary referrals differs drastically between European countries (e.g. Austria has one of the highest proportion of secondary referrals in Europe). The shift in the age of the TBI population in the last decades toward older patients (25-30% of age 65 or older; median age doubled; percentage of patients above 50 years increased 3-fold) is accompanied by the co-existence of severe systemic diseases in about 10% of the TBI population. More than 5% of patients are on anticoagulants and about 10% on platelet aggregation inhibitors. Regarding the cause of TBI, the falls are the most common problem in Europe (45-50%) and TBI-related falls occur in positive correlation with increasing age. The alcohol consumption causes overall about 20% of TBIs (with 50% of violent cases and 25% of incidental falls). Over 90% of patients in the ER and admission strata are so-called mild TBI patients. Interestingly, 36% of patients admitted primarily to the ICU could be classified as mild TBI. Concerning the 6-month GOSE outcome, 30% of patients from the ER stratum (discharged home) have not attained good recovery (**Fig. 3**). This often reflects the fact that 30% of patients with the normal CT scan on presentation (and routinely discharged home) have lesions identified only in the MRI (even more with DTI).



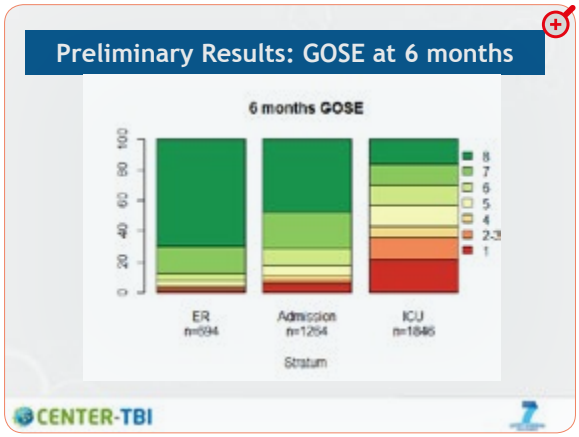


Fig. 3. The 6-month GOSE outcome in patients from ER, admission and ICU strata

The observed mortality rate in the moderate and severe TBI patients was lower than predicted (34% vs predicted 40%), and there was no difference in the functional outcome between these groups.

Dr. Mass indicated that ongoing work in the area of biomarkers will give us further insight into the complex picture of TBI in Europe. For example, improved classification and identification of patients with mild TBI should soon be possible. Overall, the results of the CENTER-TBI project are expected to improve the outcome of TBI patients by three major pathways: precision medicine, identification of best practices, and prevention with improved prognostic models.

Efficacy of Cerebrolysin in severe Traumatic Brain Injury: A multi-center, retrospective cohort study

Lynne Lucena

Bicol Regional Training and Teaching Hospital, Albay, Philippines

ABSTRACT:

Background: Severe traumatic brain injury patients with non-operative lesions are known to have a poorer prognosis. Recent modalities are now exploring the utility of Cerebrolysin in improving patient outcomes among TBI patients. However, limited studies are available showing the efficacy of Cerebrolysin among severe TBI patients.

Objectives: To determine the effects of Cerebrolysin as add-on therapy to the standard medical decompression protocol for non-operative severe TBI patients.

Methodology: The study employed a retrospective cohort design. In addition to the current medical decompression protocol for severe TBI, 42 patients received 30 ml/day CBH for 14 days followed by a subsequent dosage of 10 ml/day for another 14 days. Meanwhile, 45 patients with the same GCS range on admission but was not given CBH served as the comparison group. Primary outcomes evaluated were the proportion of patients achieving a GCS ≥9 and GOS ≥4 at Day21. Stata MP version 14 was used for data analysis.

Results: As compared to the no-Cerebrolysin group, a significantly higher proportion of patients given Cerebrolysin patients achieved a GCS ≥9 and GOS ≥4 at Day 21. Improvement in GCS is significantly higher in the Cerebrolysin group at all follow-up times. Mean length of hospital stay(LOS) is 6 days shorter in the Cerebrolysin group, and a lower proportion of Cerebrolysin patients have a LOS ≥30 days (CBH: 5% vs. No CBH: 51%).

Conclusion: Cerebrolysin is beneficial for severe TBI patients with non-operative lesions as evident by higher improvement in GCS/GOS and shorter length of hospital stay as compared to standard treatment alone.

The neurotrauma is a growing medical problem globally, and in spite of the new sophisticated technology developed for TBI management in recent years, we are losing the battle at the epidemiological scale. In 2017, the Global Burden of Disease Study (GBD) recorded 195 million new cases of road injuries worldwide, the majority of which were due to motor vehicle and motorcycle accidents (MVC). Among 15-29 years old, road traffic injuries are considered to be the leading cause of death globally. This is an exceptionally serious matter in countries like Phillippines, where 500 neurologists and 145 neurosurgeons work in a population of 105 million inhabiting 7641 islands. In 2016 alone, there were 28694 motorcycle-related injuries. The death toll was high reaching 11264, with 50% accounted for by two- or three-wheeled vehicle accidents. In people under the age of 24, this is currently the leading cause of death. An estimated 2.6% of GDP is lost due to the consequences of road traffic accidents in the Philippines.

The primary injury in the severe TBI is considered irreversible and the major point of medical management in the acute phase remains prevention of secondary injuries. Medical decompression with the hyperosmolar solution (e.g. mannitol) is recommended for relieving the intracranial pressure (ICP) and recovery of impaired cerebral perfusion. In the search for new effective therapies that could be administered to the majority of TBI victims, Dr. Lucena and her colleagues turn to agents with pharmacological profiles suitable for this fragile population. Cerebrolysin is a safe neurotrophic agent stimulating new neural connections, increasing synaptic density, regulating inflammatory processes and immune response within the injured brain. The objective of the presented study was to determine the effects of Cerebrolysin as an add-on therapy to the standard medical decompression protocol for non-operative severe TBI patients. The study employed a retrospective cohort design. In addition to the medical decompression protocol, 42 patients received 30 ml/day Cerebrolysin for 14 days followed by a subsequent dosage of 10 ml/day for another 14 days. 45 patients with the same GCS range on admission, but without Cerebrolysin treatment protocol were considered for the comparison/control group. As a primary outcome, the proportion of patients achieving a GCS ≥9 and GOS ≥4 at day 21 was calculated. Stata MP version 14 was used for data analysis.

Dr. Lucena presented the demographic data of the patients' population and went on to discuss the results of the study. Treatment with Cerebrolysin resulted in a significantly higher proportion of patients shifting to mild and moderate TBI categories (GCS ≥9) on day 21, in comparison with the control group. Also, the proportion of patients with improved outcomes favored Cerebrolysin treatment on day 21 (**Fig. 1**).

Among the patients who survived up to day 21, the mean length of hospital stay (LOS) was significantly shorter in the Cerebrolysin group in comparison with the control group (Cerebrolysin 25.61 ± 3.24 vs. control 31.92 ± 7.30, p<0.00001). All patients in the Cerebrolysin group were discharged from the hospital within 33 days as compared to 47 days for the control group. Further analysis revealed that the proportion of patients with LOS of ≥30 days is significantly lower in Cerebrolysin versus the control group (Cerebrolysin 5% vs. control 51%, p<0.00001). The sensitivity analyses revealed that improvement in GCS from day 7 to 21 was found to be significantly higher in the Cerebrolysin group, but only for younger patients (<40 years). In terms of diagnosis, improvement in GCS was not statistically different between Cerebrolysin and the control groups among diffuse cerebral edema (DCE), epidural hematoma (EDH) and post-traumatic subarachnoid hemorrhage (SAH) patients. The difference in the proportion of patients achieving a score of GCS ≥9 was significant between the two groups for patients diagnosed with intracerebral hematoma (ICH). All Cerebrolysin treated patients diagnosed with cerebral contusion (CC) and diffuse axonal injury (DAI) achieved GCS ≥9 on day 21.

Concluding her lecture, Dr. Lucena indicated that this retrospective study provided preliminary evidence that Cerebrolysin is beneficial for severe TBI patients with non-operative lesions. Although patients without Cerebrolysin also showed a significant increase in GCS scores over time, the improvement in GCS from day 7 to 21 was consistently higher in the treated patients. The patients showed faster recovery rates as inferred from the greater improvement in GCS/GOS as well as from a shorter duration of hospital stay in comparison to the standard of care. Furthermore, above 90% of patients presenting with a cerebral contusion, diffuse axonal injury, and intracerebral hematoma showed favorable GCS on day 21. It remains to be seen if the observed treatment benefits can be maintained over a longer period.

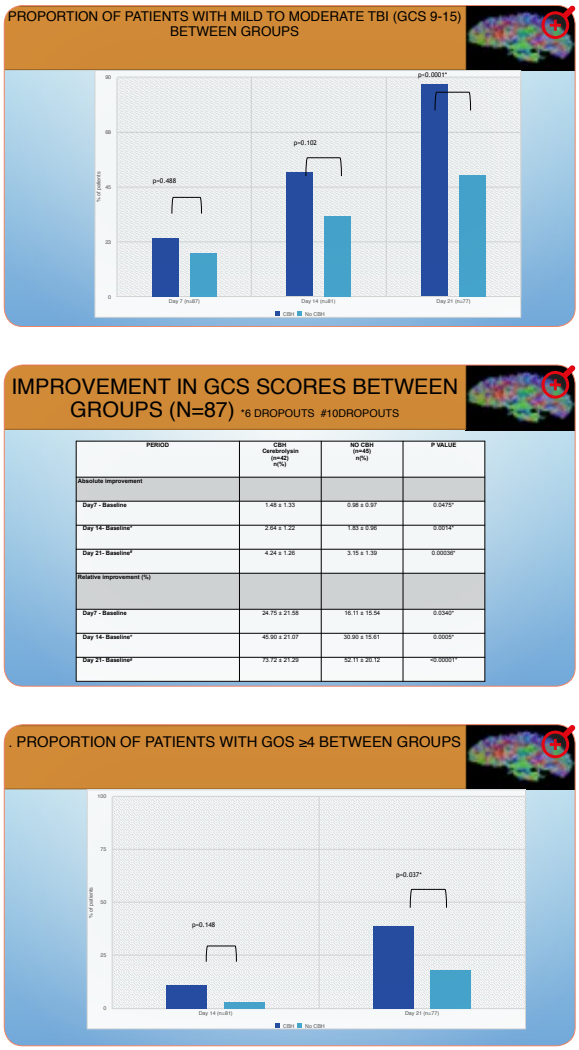


Fig. 1. The improvement of severe TBI patients after treatment with Cerebrolysin

New perspectives for Traumatic Brain Injury: Results from the CAPTAIN trial series and meta-analysis

Dafin Muresanu

Chairman Department of Neurosciences, University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania

ABSTRACT:

Traumatic brain injury (TBI) is a multifaceted condition that encompasses a broad clinical and disability spectrum, determined by a myriad of potential injuries, cellular pathways, genetic phenotypes, and environmental factors. Previous clinical trials have failed to highlight the efficacy of pharmacological interventions.

The complexity of TBI is reflected in the low assay sensitivity for conventional research methods that involve arbitrary dichotomization of outcome scales. We explored the efficacy of the multimodal agent Cerebrolysin for recovery after TBI using a multidimensional approach.

CAPTAIN I and CAPTAIN II are randomized, double-blind, placebo-controlled trials that enrolled patients with moderate to severe TBI (Glasgow Coma Scale score 6-12). A meta-analysis was also performed using stochastic ordering, fixed effects, random effects and a combined model using the Wei-Lachin pooling procedure.

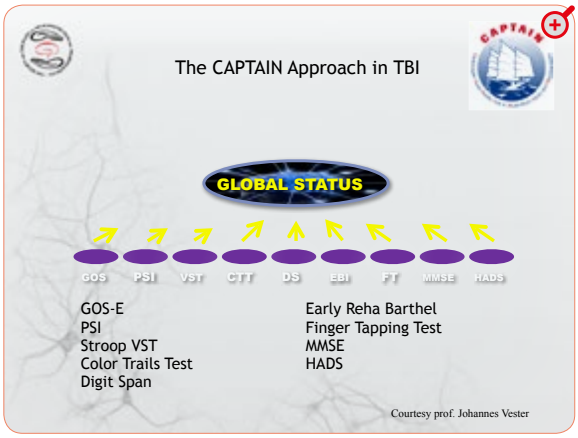
Both trials results reveal high assay sensitivity of the multidimensional approach, indicating benefits of Cerebrolysin at Day 30 and 90 intention- to-treat populations. The baseline prognostic risk score shows excellent comparability between treatment groups (median = 2.0; MW = 0.4883). The meta-analysis of the trial series shows statistically significant superior- ity of Cerebrolysin at 30 and 90 days after TBI regardless of methodology (stochastic ordering, fixed and random effects), indicating no observed heterogeneity (I-Square=0.0%).

The CAPTAIN trial series and meta-analysis indicate the efficacy of Cerebrolysin for moderate to severe TBI recovery and confirm the agent's excellent safety profile. We discuss these results to showcase major clinical implications for treatment and methodological breakthroughs in TBI research.

Dr. Muresanu dedicated his lecture to discussing therapeutic ideas with future clinical potential. There are two prevailing approaches in the development of new treatments for TBI and both can be derived from pathophysiological observations and patients' profiles. A frequently observed progression of contusive brain injury (particularly, through inflammatory processes) defines the first subpopulation of TBI patients. They are more likely to benefit from acute neuroprotection strategies (in the classical sense) with the potential to limit processes involved in secondary brain damage. The strategies and therapies aimed at promoting regeneration or replacement of lost neurons, glial cells, neuronal circuits, and stimulation of neuroplasticity (neurorecovery strategies) may be more suited for the second subpopulation of patients; those with diffuse axonal injury (DAI).

Understanding post-lesional brain regulation is required for advancement in this therapeutic field. After an acute brain injury, an endogenous brain defense response is triggered consisting of two principal anti-correlated mechanisms. An immediate one is aimed at the reduction of brain damage and impairment (endogenous neuroprotection) and lasts hours to 2-3 days. The subsequent one is directed at repairing the damaged brain and reducing disability (endogenous neurorepair), through highly regulated neurotrophic, neuroplasticity, and neurogenic processes. The higher is the intensity of neuroprotection, the lower is the output of regeneration. With elapsing time, the capacity of neuroprotection is declining while the regenerative processes intensify and last for weeks and months after the primary injury. Consequently, neurorepair processes account for up to 80% of the total functional recovery. Our knowledge about previously identified pathophysiological events (e.g. excitotoxicity, inflammation, apoptosis) has also evolved. They represent but imbalances of normal physiological processes. This means, that they should not be targeted with blockers or inhibitors (so-called monomodal, suppressive neuroprotective agents). These strategies were used in the past and all failed in the clinical trials. Likewise, simple stimulation of neuroplasticity (with so-called monomodal pleiotropic agents) during neurorehabilitation can lead to undesired side effects. The effective therapies should modulate and re-balance, rather than inhibit, acting through endogenous biological mechanisms of neuroprotection and neurorepair. Such a therapeutic strategy should employ so-called multimodal agents with a proven safety profile (e.g. Cerebrolysin).

The failure of past clinical trials in TBI reflects both poor understanding of the pathophysiology of brain recovery (e.g. choice of blockers for neuroprotection), and problems with the clinical trial methodology. Customary, a recombinant clinical trial (RCT) in TBI would employ a single assessment scale (usually GOS) and use the dichotomization of the outcome to feed the statistical analysis. The choice of the outcome scale and the cutoff outcome point for dichotomization on that scale was made arbitrarily. This methodological paradigm led to misleading and opposing conclusions about the efficacy and clinical utility of the investigated treatments. Valuable efficacy data could have been lost in the process. Additionally, the use of a single scale poorly reproduced the reality of TBI. Dr. Muresanu underlined that we have learned our lesson from the past, as expressed in the recommendations of various expert panels, including the IMPACT group (Maas et al., 2010): "Outcome after TBI is by definition multidimensional including neuro-physical disabilities and disturbances in mental functioning". Accordingly, in TBI trials, we must use multiple scales assessing various neurological parameters. To be able to properly process and interpret the complex data gathered through a multidimensional approach, the multivariate statistical analysis has been proposed. Using this method (Wei-Lachin procedure), the appropriate correlation among the respective endpoints is calculated and the efficacy conclusion is expressed as a global score.



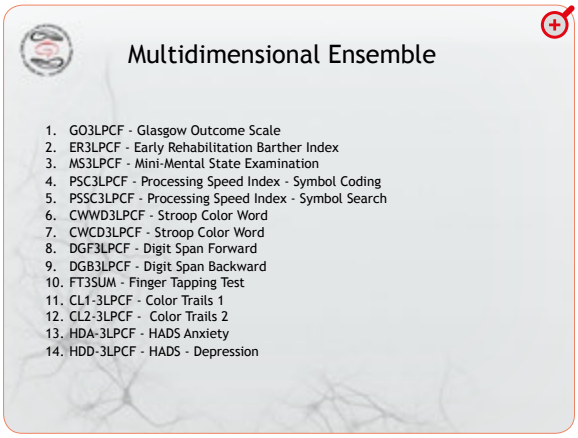


Fig. 1. The multivariate analysis of multiple outcome scales in the CAPTAIN trial series

Dr. Muresanu introduced the audience to CAPTAIN trials series, representing the first attempt to employ the new multidimensional approach based on full (not dichotomized) outcome scales in TBI research (**Fig. 1**).

One of the major issues in clinical development is the inherent heterogeneity of the TBI patients population. In the CAPTAIN trials, the patients' stratification and inclusion strategy reflected the newest recommendations (Hukkelhoven et al., 2005; Maas et al., 2005) and employed the Baseline Prognostic Risk Score (BPRS) instead of Glasgow Coma Scale (GCS).

The CAPTAIN I was conducted in Asia-Pacific and was terminated prematurely (ITT = 40) due to the poor adherence to the complex trial protocol in the Chinese centers. Nevertheless, the investigators analyzed available results to assess the practicality of the design and to inform a decision about the continuation of the project. The baseline comparability was very good for the included study population as was the safety of the treatment. The results of the study have just been published in the journal Neurological Sciences (Poon et al., 2019).

The per-protocol population analysis on day 30 and day 90 revealed a positive statistical trend in the global score for the Cerebrolysin group as well as high resolution of the multivariate analysis (**Fig. 2a**). This encouraged the continuation of the project with the follow-up CAPTAIN II trial conducted in Romania on a larger population. To further test the CAPTAIN design, the investigators used the same model but conducted the trial in a single center for even better control of the heterogeneity within the study population, and for decreasing the time-to-needle from 6 to 4 hours. The results confirmed the positive, statistically significant global score for the treated group (**Fig. 2b**). Further meta-analysis corroborated the results of the two trials (**Fig. 2c**) for both day 30 and day 90 endpoints. These results should encourage wider application of the new multidimensional methodology in TBI research.

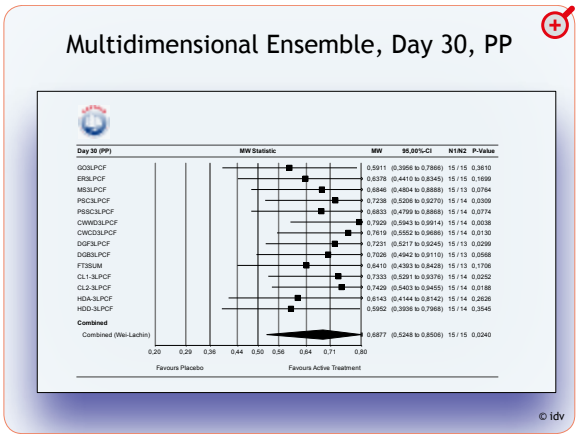


Fig. 2a. The results of the CAPTAIN I

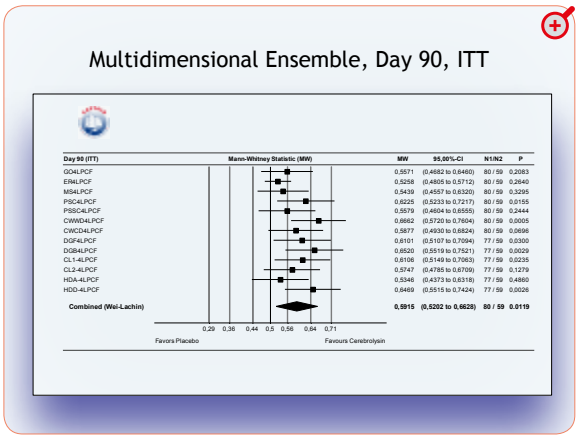


Fig. 2b. The results of the CAPTAIN II

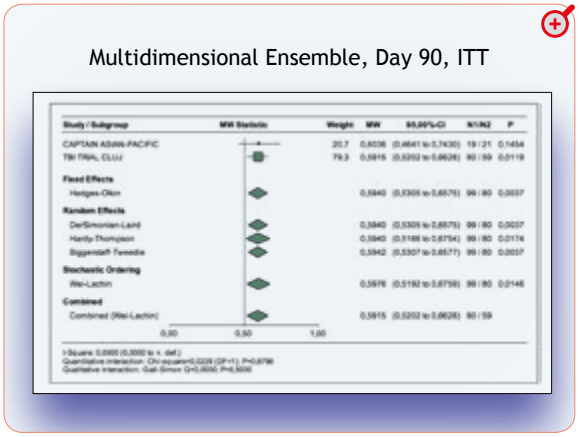


Fig. 2c. META-ANALYSIS

Cerebrolysin for treatment of aneurysmal SAH in adults: A retrospective review with reference to unanticipated late effect

Hyeong-Joong Yi

Hanyang University Medical Center, Seoul, Korea

ABSTRACT:

Cerebrolysin is a neuroprotective drug used in the treatment of acute ischemic stroke. To our knowledge, this drug has never been evaluated in patients with aneurysmal subarachnoid hemorrhage (SAH). The aim of this study was to evaluate the effect of Cerebrolysin in patients with aneurysmal SAH.

Aneurysmal SAH patients who had their aneurysm obliterated at our institution from 2007 to 2016 were retrospectively studied. Patients received Cerebrolysin treatment or standard care only (control group). Subgroup analyses were performed according to Hunt and Hess grade (good grade≤ 2, N= 216; poor grade≥ 3, N= 246) and treatment procedure (clip or coil). In good-grade patients (N = 216), clinical outcomes and mortality did not differ significantly between the control and Cerebrolysin groups. In poor-grade patients (N = 246), the mortality rate was significantly lower in the Cerebrolysin group (8.7%) than in the control group (25.4%, p= 0.006). In patients who received microsurgical clipping (N = 328), the mortality rate was significantly lower in the Cerebrolysin group (7.3%) than in the control group (18.5%, p= 0.016).

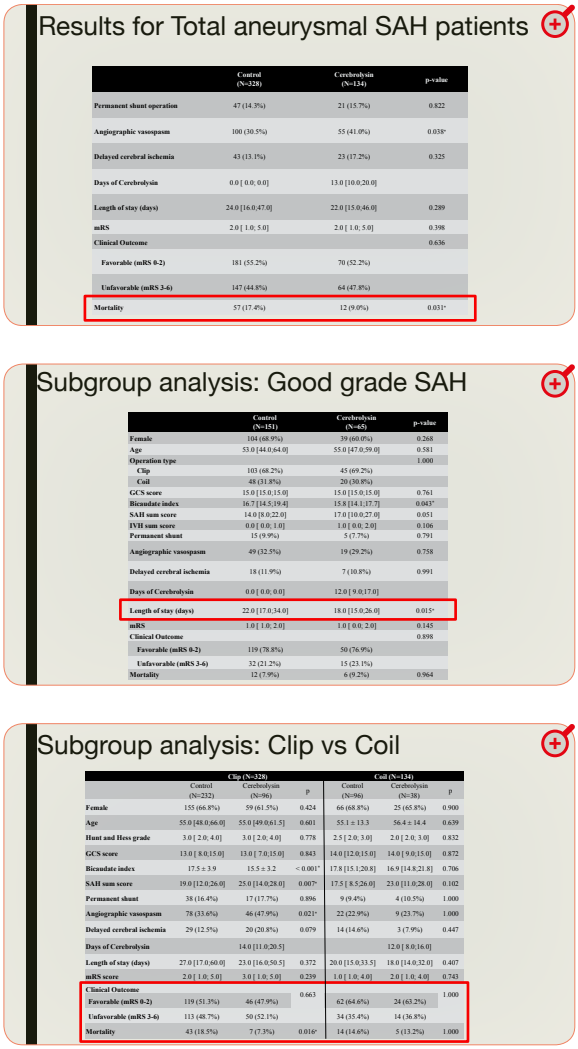
Cerebrolysin injection during the acute period of SAH appeared to reduce the mortality rate, especially in poor-grade patients. This study suggests the potential of Cerebrolysin for treating aneurysmal SAH. Further studies are needed to confirm our results.

As a neurosurgeon with extensive experience in managing aneurysmal SAH, Dr. Yi stated that there is no particular agent that can prevent the negative secondary consequences of this kind of catastrophic injury. Cerebrolysin is known in Korea for the treatment of various post-operative neurological lesions, mainly after TBI, but also for the treatment of patients with dementia and ischemic stroke. However, no experience has been gathered in the field of hemorrhagic stroke. This project aimed at investigating the potential benefits of Cerebrolysin treatment in this group of patients, with a focus on the SAH group. Daily doses of 30ml Cerebrolysin diluted in 100ml normal saline were administered as a slow intravenous infusion over 24 hours. The treatment was initiated within 48 hours after aneurysmal SAH and lasted for a minimum of 3 days. This was a retrospective medical records review conducted for at least 6 months in a single institution, Hanyang University Medical Center in Seoul (Korea). From 130 to 150 surgical cases of aneurysm (clipping: coiling ratio was 4:6) per year had been managed in this institution in recent years. The study included patients with SAH who underwent immediate aneurysmal occlusion and lasted until December 2016. The Control group (N = 328) was treated with traditional triple H therapy (hypotension, hemodilution, and hypovolemic management), while the study group (N = 134) was treated with Cerebrolysin alone for an average of 15 days. The results of the study were published last year (Park et al., 2018).

There were no significant baseline differences identified between the study groups at inclusion. The mortality was significantly higher in the Control group in comparison with Cerebrolysin group (17.4% vs 9% respectively, P = 0.031). After stratification of the patients according to the severity score, the mortality rate among the patients with the poor Hunt and Hess grade (3 and higher) was significantly lower in Cerebrolysin group than in the Control group with the same score (8.7% vs 25.4% respectively, P = 0.006). In the subgroup of patients with the good Hunt and Hess grade (2 and below), this difference was unclear. In the same subgroup, the length of hospital stay was significantly shorter for the Cerebrolysin group (18 vs 22 days, Cerebrolysin vs Control, P = 0.015). Additional subgroup analysis divided the patients into microsurgical clipping group (Cerebrolysin, N = 96 vs. Control, N = 232) and endovascular coil embolization group (Cerebrolysin, N = 38 vs. Control, N = 96). The mortality rate was significantly lower in the clipping group treated with Cerebrolysin vs Control (7.3% vs 18.5% respectively, P = 0.016). There was no significant difference in mortality rate between groups in the coiled population (13.2% Cerebrolysin vs 14.6% Control). The adverse effects were equally distributed in

the study population. In summary (**Fig. 1**), the results showed that for the good grade SAH patients Cerebrolysin did not improve the clinical outcome, although the treatment shortened significantly the length of hospital stay. Among the poor grade SAH patients, Cerebrolysin significantly lowered the mortality rate. The same was true for the patients undergoing microsurgical clipping procedure.

Dr. Yi proposed potential mechanisms through which Cerebrolysin impacts SAH patients. Cerebrolysin appears to inhibit brain edema and inflammatory response after intracranial hemorrhage. This suggestion was confirmed by the recently published results of the experimental study by Yang et al., 2016. Both experimental and clinical results suggest that Cerebrolysin has the potential for reducing the mortality rate among SAH patients. In light of these promising results, a new prospective multicenter RCT was launched in Korea and is currently underway. The investigators are also planning to widen up the use of Cerebrolysin in hemorrhagic stroke to include patients with intracerebral hemorrhage, fatal cerebral infarction, and severe brain edema. Further clinical studies are mandated for the assessment of Cerebrolysin benefits in TBI patients.



	Control (N=328)	Cerebrolysin (N=134)	p-value
Permanent shunt operation	47 (14.3%)	21 (15.7%)	0.822
Angiographic vasospasm	100 (30.5%)	55 (41.0%)	0.038*
Delayed cerebral ischemia	43 (13.1%)	23 (17.2%)	0.325
Days of Cerebrolysin	0.0 [0.0; 0.0]	13.0 [10.0;20.0]	
Length of stay (days)	24.0 [16.0;47.0]	22.0 [15.0;46.0]	0.289
mRS	2.0 [1.0; 5.0]	2.0 [1.0; 5.0]	0.398
Clinical Outcome			0.636
Favorable (mRS 0-2)	181 (55.2%)	70 (52.2%)	
Unfavorable (mRS 3-6)	147 (44.8%)	64 (47.8%)	
Mortality	57 (17.4%)	12 (9.0%)	0.031*

	Control (N=151)	Cerebrolysin (N=45)	p-value
Female	104 (68.9%)	39 (60.0%)	0.268
Age	53.0 [44.0;64.0]	55.0 [47.0;59.0]	0.581
Operation type			1.000
Clip	103 (68.2%)	45 (69.2%)	
Coil	48 (31.8%)	20 (30.8%)	
GCS score	15.0 [15.0;15.0]	15.0 [15.0;15.0]	0.761
Bicaudate index	16.7 [14.5;19.4]	15.8 [14.1;17.7]	0.043*
SAH sum score	14.0 [8.0;22.0]	17.0 [10.0;27.0]	0.051
IVH sum score	0.0 [0.0; 1.0]	1.0 [0.0; 2.0]	0.106
Permanent shunt	15 (9.9%)	5 (7.7%)	0.791
Angiographic vasospasm	49 (32.5%)	19 (29.2%)	0.758
Delayed cerebral ischemia	18 (11.9%)	7 (10.8%)	0.991
Days of Cerebrolysin	0.0 [0.0; 0.0]	12.0 [9.0;17.0]	
Length of stay (days)	22.0 [17.0;34.0]	18.0 [15.0;26.0]	0.015*
mRS	1.0 [1.0; 2.0]	1.0 [0.0; 2.0]	0.145
Clinical Outcome			0.898
Favorable (mRS 0-2)	119 (78.8%)	50 (76.9%)	
Unfavorable (mRS 3-6)	32 (21.2%)	15 (23.1%)	
Mortality	12 (7.9%)	6 (9.2%)	0.964

	Clip (N=328)			Coil (N=134)		
	Control (N=232)	Cerebrolysin (N=96)	p	Control (N=96)	Cerebrolysin (N=38)	p
Female	155 (66.8%)	59 (61.5%)	0.424	66 (68.8%)	25 (65.8%)	0.900
Age	55.0 [48.0;66.0]	55.0 [49.0;61.5]	0.601	55.1 ± 13.3	56.4 ± 14.4	0.639
Hunt and Hess grade	3.0 [2.0; 4.0]	3.0 [2.0; 4.0]	0.778	2.5 [2.0; 3.0]	2.0 [2.0; 3.0]	0.832
GCS score	13.0 [8.0;15.0]	13.0 [7.0;15.0]	0.843	14.0 [12.0;15.0]	14.0 [9.0;15.0]	0.872
Bicaudate index	17.5 ± 3.9	15.5 ± 3.2	< 0.001*	17.8 [15.1;20.8]	16.9 [14.8;21.8]	0.706
SAH sum score	19.0 [12.0;26.0]	25.0 [14.0;28.0]	0.007*	17.5 [8.5;26.0]	23.0 [11.0;28.0]	0.102
Permanent shunt	38 (16.4%)	17 (17.7%)	0.896	9 (9.4%)	4 (10.5%)	1.000
Angiographic vasospasm	78 (33.6%)	46 (47.9%)	0.021*	22 (22.9%)	9 (23.7%)	1.000
Delayed cerebral ischemia	29 (12.5%)	20 (20.8%)	0.079	14 (14.6%)	3 (7.9%)	0.447
Days of Cerebrolysin		14.0 [11.0;20.5]			12.0 [8.0;16.0]	
Length of stay (days)	27.0 [17.0;60.0]	23.0 [16.0;50.5]	0.372	20.0 [15.0;33.5]	18.0 [14.0;32.0]	0.407
mRS score	2.0 [1.0; 5.0]	3.0 [1.0; 5.0]	0.239	1.0 [1.0; 4.0]	2.0 [1.0; 4.0]	0.743
Clinical Outcome			0.663			1.000
Favorable (mRS 0-2)	119 (51.3%)	46 (47.9%)		62 (64.6%)	24 (63.2%)	
Unfavorable (mRS 3-6)	113 (48.7%)	50 (52.1%)		34 (35.4%)	14 (36.8%)	
Mortality	43 (18.5%)	7 (7.3%)	0.016*	14 (14.6%)	5 (13.2%)	1.000

Fig. 1. The results of the retrospective review of Cerebrolysin treatment in SAH patients

Pathophysiological basis of post ICU syndrome: the role of neurothrophic factors

Martin Carreras

JMaimonides University, Buenos Aires, Argentina

ABSTRACT:

In the last quarter-century, the description of the post-intensive care unit syndrome has led to a wider recognition of the prolonged disease burden affecting critical illness survivors. Prolonged physical disability, neuropsychiatric morbidity, and cognitive impairment have been recognized as its hallmark features.

A correlation between the degree of brain injury and prolonged cognitive impairment has been observed, and several secondary brain injury factors have been associated with the cognitive impairment that may follow critical illness. All of these factors are believed to overwhelm the natural defense mechanisms of the neurovascular unit through various pathways, impairing the mechanisms that promote neuroplasticity, neuroprotection and neurogenesis in the central nervous system.

Over the last years, research has established new muscle-brain interactions that may serve to potentiate these natural neuroprotective mechanisms through neurotrophic and anti-inflammatory signaling pathways, as well as the beneficial effects of "synthetic" neurotrophic factors such as Cerebrolysin in the context of primary brain injury in dementia, stroke, and traumatic brain injury.

These appear as promising avenues of research to help prevent and reduce the burden of cognitive impairment following critical illness, as well as potentially beneficial agents for the cognitive rehabilitation of critical illness survivors.

The post-ICU syndrome is defined as a collection of symptoms including physical disability and impairment (ICU acquired weakness), neuropsychiatric disorders (depression, anxiety, PTSD), and cognitive impairment (new or worsened). Early retrospective studies of the ARDS network published in the late nineties suggested the causative relationship between ICU and cognitive decline. This link was further confirmed and defined in the prospective BRAIN-ICU study by the Vanderbilt group of Wes Ely (Pandharipande et al., 2013). The patients admitted to ICU for causes unrelated to brain injury and without a history of cognitive impairment were developing symptoms of dementia 3 and 12 months after the discharge from ICU. About 40% of all patients developed cognitive impairment similar to moderate or severe TBI, while a quarter of patients showed symptoms comparable to mild Alzheimer's disease. Why then our patients have symptoms of brain injury after ICU if they were admitted to ICU without brain injury? Asked Dr. Carreras.

In the past, neurovascular unit disfunction has been associated with a wide array of CNS diseases and in all those cases the BBB malfunction and neuroinflammation were evident. The post-mortem brain examination of patients after ICU, TBI, stroke and various neurodegenerative diseases all reveal common hallmarks of BBB dysfunction: cerebral edema, ischemic lesions, hemorrhages, microthrombi and microabscesses, leukoencephalopathy. As seen in the imaging analysis, the increased brain atrophy, decreased volumes of the superior frontal lobes, thalami, and cerebellum and alterations in tractography in the anterior internal capsule and knee of the corpus callosum were all correlated with cognitive decline after ICU. Among the known modifiable risk factors for cognitive decline after ICU delirium appears to be the most prominent. Several biomarkers associated with cognitive impairment after ICU have been identified, including: S100B (marker of BBB dysfunction/astrocyte injury), E-selectin (cell adhesion molecule involved in leukocyte adhesion and activation), UCHL1 (marker of acute neuronal damage, important factor in the ubiquitin-proteasome system), BDNF (the most abundant neurotrophin, with a key role in neuroplasticity), PAI-1 (plasminogen activator inhibitor), and IL-6 (pro-inflammatory cytokine and marker of inflammation). The picture emerging from the research suggests a combination of brain inflammation and BBB dysfunction as important pathophysiological mechanisms leading to cognitive impairment after ICU. The malfunctioning of the neurotrophic regulation is another important hallmark of the cognitive decline across various disorders, including ICU-acquired. Neurotrophic factors are the principal mediators of neuronal survival and regeneration in the CNS. Re-establishment of the neurotrophic regulation in the injured brain could counteract the processes leading to cognitive decline.

Dr. Carreras discussed two therapeutic strategies aimed at counteracting the pathophysiological hallmarks of cognitive decline: physical exercise and neurotrophic therapy. The first strategy relates to muscle-brain interaction and the role of the muscular system as an endocrine organ. The relationship between the sedentary lifestyle or immobilization with the increased inflammatory processes and chronic diseases is well established, as is the link between the active lifestyle and improved metabolic, neuromuscular and neurological performance (**Fig. 1**).

Several studies have linked high levels of physical exercise with hippocampal size and cognitive measures, suggesting that exercise leads to anatomical and physiological alterations in the brain across all age groups. Aerobic fitness reduces aging-related brain tissue loss, especially in the prefrontal, superior parietal and temporal cortices, as well as the anterior and transverse tracts between frontal and posterior parietal lobes. Moderate exercise reduced the progression of disability in activities of daily living by 1/3 in a nursing home population with Alzheimer's disease after 12 months. A meta-analysis of exercise training in patients with cognitive impairment and dementia demonstrated a positive effect on functional performance, behavioral measures, and cognitive tasks. A meta-analysis by Northley (2018; with data from 36 studies) concluded that physical exercise is effective at improving the cognitive function of adults over-50, regardless of their basal cognitive aptitude. The modes that demonstrated a positive effect were aerobic exercise, resistance exercise, and tai chi. The effect of exercise on cognition was significant for all domains except global cognition, with the highest impact on executive function, memory, and working memory. The neurotrophic regulatory pathway appears to be closely associated with these effects. It was found that insulin-like growth factor 1 (IGF-1) induced by physical exercise promotes neurogenesis in the dentate gyrus and also induces brain derived neurotrophic factor (BDNF) expression in the hippocampus. BDNF is the most widely expressed neurotrophin that modulates neuronal survival, differentiation,

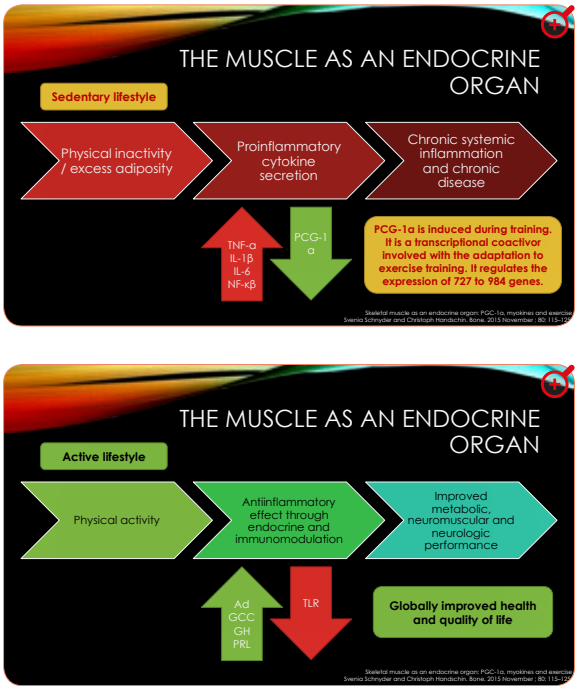


Fig. 1. The muscular system as an endocrine organ

axonal-pathfinding, induces and maintains LTP, and has an anti-apoptotic impact. Its expression is induced through several pathways during physical exercise. On the other hand, the neuroprotective functions of the muscular system have been linked with anti-inflammatory processes mediated by several molecular mechanisms, including interleukin 6 (IL-6) mediated pathway. Dr. Carreras suggested that the results of extensive basic research point to a dual anti-inflammatory and neurotrophic-mediated action of the physical exercise. This led recently to the hypothesis that physical exercise can be employed as a means of neuroprotection in various neurological diseases, including in ICU patients. The ABCDEF bundle emerged as an evidence-based guideline to optimize patient care and to improve patient recovery and outcomes after ICU. Two key parts of the bundle are an assessment of delirium and early mobilization. Prevention of delirium appears to be vital for ameliorating cognitive decline after ICU. Early mobilization is currently recommended as the only intervention that has demonstrated a decrease in the days of delirium. Similarly, early mobilization is recommended, by the relevant stroke treatment guidelines, for improved recovery of stroke patients.

The dual pharmacological plus physical exercise strategy for the prevention of the cognitive decline in the ICU patients appears to be mandated. Several experimental studies showed already promising results. For example, in a stroke model, exercise combined with low levels of $GABA_A$ receptor inhibitor potentiated the expression of BDNF in the motor cortex and improved motor function when compared to exercise alone. Nogo is a family of growth-inhibiting factors that inhibits neuronal plasticity. It is upregulated after CNS injury. Exercise reduced the expression of Nogo-A after stroke, and, when combined with anti-Nogo-A therapy, it led to improved cognitive and motor recovery.

Cerebrolysin is a well known neurotrophic agent used in the treatment of Alzheimer's disease, vascular dementia, TBI and stroke. Dr. Carreras outlined the available clinical data for Cerebrolysin that were summarized in recent meta-analyses (**Fig. 2**).

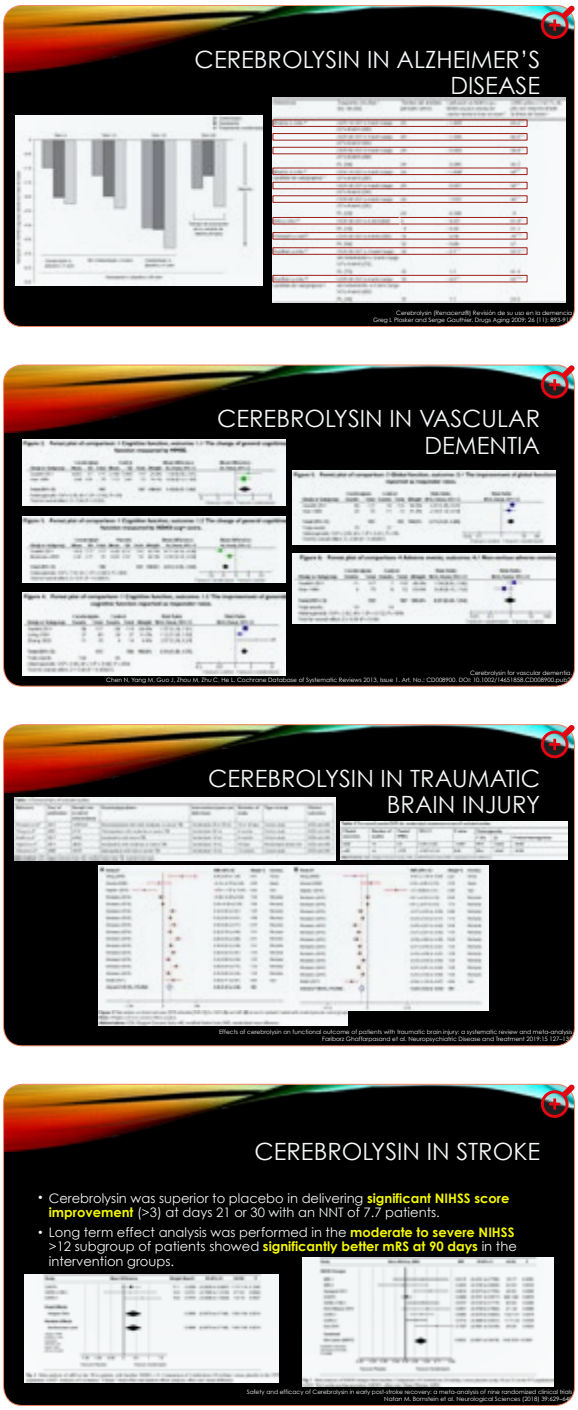


Fig. 2. The neurotrophic treatment with Cerebrolysin for the prevention of the cognitive decline in various CNS diseases

Placebo-controlled trials showed significant and consistent improvement in global cognition (CIBIC+ and CGIS/S) in mild and moderate Alzheimer's disease. In the subgroup of severely affected patients, there was a significant improvement in ADAS-cog and ADAS-cog+. A study evaluating treatment with Cerebrolysin and donepezil showed improvement in ADAS-cog+ at 28 weeks both with donepezil and Cerebrolysin, but greater benefits were observed with the combined treatment. At 48 weeks, CIBIC+ testing was significantly better in the Cerebrolysin group vs donepezil. Neuropsychiatric symptoms improved in the three intervention groups in a similar fashion. A trial of Cerebrolysin and rivastigmine showed no improvement at 24 weeks with rivastigmine, whereas there was a significant improvement with Cerebrolysin in ADAS-cog and IADL testing. At the end of each cycle of the Cerebrolysin regimen, there was a significant improvement in MMSE, ADAS-cog, and IADL. In vascular dementia, Cerebrolysin had a beneficial effect on general cognitive function as measured by MMSE and ADAS-cog+. Improved WISA scores were still significantly better with Cerebrolysin even after 3 years. Cerebrolysin also significantly improved executive function as measured with Clock-drawing and Trail-making tests. The treatment group was superior vs. placebo group in the improvement of global clinical function as measured by ADL, NAI and SCAG scores. The Cochrane review concluded that Cerebrolysin may have positive effects on the improvement of cognitive and global function in elderly patients with mild to moderate vascular dementia, but given the limited number of trials, variable treatment duration and short-term follow up there is still insufficient evidence to recommend Cerebrolysin as routine treatment for vascular dementia. In a recent meta-analysis of TBI studies, Cerebrolysin was superior to placebo, showing significantly higher GOS scores in patients with TBI, and lower mRS at the end of treatment. The benefits of Cerebrolysin were most evident in the moderate and severe TBI subgroups. In a stroke, the most recent study (Stan et al., 2017) demonstrated the superiority of Cerebrolysin + early physical neurorehabilitation (after 10 days of treatment) at 30 days, with significantly better mRS, Barthel Index and NIHSS in the treatment group. At 30 days, 73% of patients in the Cerebrolysin group were scored 0 to 3 on mRS vs 44.8% with low mRS scores in the placebo group.

Dr. Carreras suggested that in light of this clinical evidence and the outlined here scientific rationale Cerebrolysin appears to be a good candidate as a treatment for the prevention of the cognitive decline in the ICU patients, including in combination with physical exercise and early mobilization. However, no studies were performed with Cerebrolysin in this clinical context and it remains to be seen if Cerebrolysin can bring benefits also in this group of patients.

Best practices for Post-TBI rehabilitation programs

Mark Bayley

UHN-Toronto Rehabilitation Institute, Toronto, Canada

ABSTRACT:

Brain injury results in significant changes in cognitive-behavioural and physical function that may have a long-term negative impact on quality of life for patients and their families. It is critical that these individuals get the most current Neurorehabilitation after Traumatic Brain injury. It is very challenging for clinicians to keep up with their expanding evidence.

Best practice guidelines have been proposed as a solution to this challenge and in this presentation, a number of freely accessible online resources will be reviewed.

These include the Ontario Neurotrauma Foundation clinical practice guidelines (www.braininjuryguidelines.org) and the Evidence-based review of Acquired Brain injury (www.abiebr.ca).

The World Health Organization rehabilitaiton evidence based recommendations will also be referenced. Key best practices for brain injury rehabilitation programs will be highlighted including some of the key components of the optimal system for inpatient and community based care and how they can be adapted to the local context in all health systems in high, middle and low income countries.

By the end of the presentation, participants should be able to:

1. Name the unique features of the INESSS-ONF Guideline for Rehabilitation after Moderate and Severe Traumatic Brain Injury
2. Identify some key best practices for Brain injury rehabilitation programs that should be included in all programs
3. Navigate the guidelines quickly using smartphone, tablet or computer to find recommendations, evidence summaries, implementation tools and measures of adherence and outcomes

In approaching the task of preparation of the Canadian TBI rehabilitation guidelines, the authors wanted to understand the needs and expectations of future users. These were identified and included priorities in the TBI rehabilitation system: (1) intensity/frequency of interventions; (2) rehabilitation models; (3) duration of interventions; and (4) continuity-of-care mechanisms. Additionally, the following sequelae needed to be addressed (1) behavioral disorders; (2) cognitive dysfunction; (3) fatigue and sleep disturbances; and (4) mental health. Accordingly, these were the issues emphasized in the INESSS-ONF guidelines (**Fig. 1**).

Dr. Bayley presented the unique features of the guidelines (the detailed description of the guidelines is published in the Journal Head Trauma Rehab, Vol. 33, No. 5, pp. 296–305).

The backbone of the guidelines is ERABI (Evidence-Based Review of Acquired Brain Injury). It is a systematic review that is ongoing already for several years, with updates made every year. The level of evidence used by various existing guidelines diverges depending on the individual methodology. To achieve consistency among the recommendations, the level of evidence for each recommendation was assigned the INESSS-ONF grade:

A – Recommendation supported by at least 1 meta-analysis, systematic review, or randomized controlled trial of appropriate size with the relevant control group

B – Recommendation supported by cohort studies that at minimum have a comparison group, well-designed single-subject experimental designs, or small sample size randomized controlled trials

C – Recommendation supported primarily by expert opinion based on their experience, though uncontrolled case series without comparison groups that support the recommendations are also classified here.

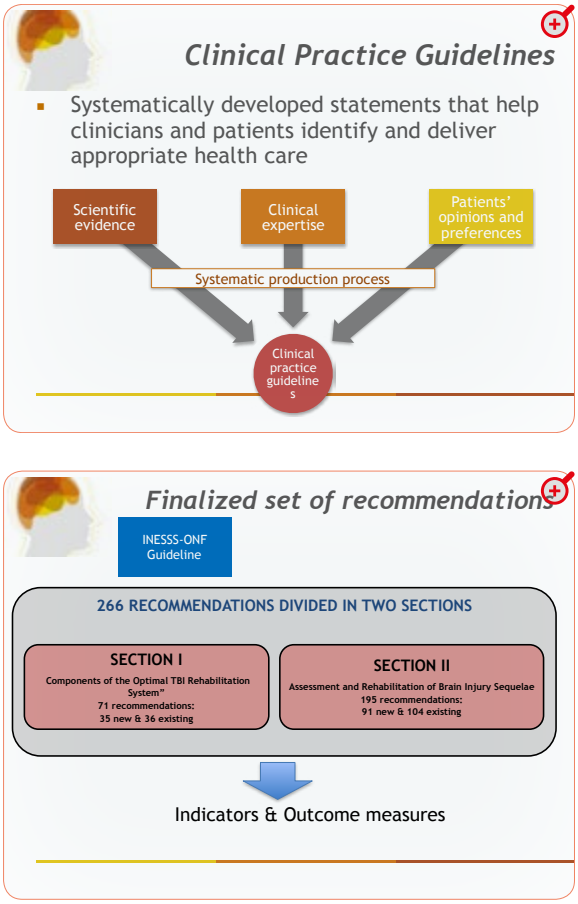


Fig. 1. The construction of INESSS-ONF Clinical Practice Guideline for the Rehabilitation of Adults with Moderate to Severe Traumatic Brain Injury

A total of 266 recommendations were divided into two sections, the first dealing with the rehabilitation system and the second dealing with the sequelae of rehabilitation in patients. The target of the first section are the health care leaders who are responsible for designing the system. The topics presented in this section cover such elements as key components of TBI rehabilitation, management of disorders of consciousness, subacute rehabilitation, promoting reintegration and participation, caregivers and families, brain injury education and awareness, capacity, and consent. The second section of the guidelines is addressed to clinicians. It provides and evaluates specific treatment strategies for complications post-TBI, like: comprehensive assessment of the person with TBI, disorders of consciousness, cognitive function, dysphagia and nutrition, motor function and control, sensory

impairment, fatigue and sleep disorders, pain and headaches, psychosocial/adaptation issues, neurobehavioural and mental health, substance use disorders, medical/nursing management.

Dr. Bayley asked the audience to navigate to the website of the guidelines and went on to present its content in an interactive fashion with the audience being able to follow his instructions on their own cellular phones (**Fig. 2**).

Dr. Bailey presented a patient's case to illustrate the flow, purpose, and logic of the INESSS-ONF guidelines. The audience was able to practice the sequence of practical steps, starting with the identification of key components of the rehabilitation most suitable for this particular patient. They could also gain insight into fundamentals (F) and priorities (P) of the rehabilitation process (in the case of the limited time available in the decision process). Subsequently, the users could see and compare grades of recommendation for each element of rehabilitation under consideration. For every recommendation, the users had direct access to the module/source from which the recommendation was derived. Finally, Dr. Bayley directed the audience to the second section of the guidelines dealing with the complications (section R), including a comprehensive chapter with access to relevant assessment tools.

Summarizing his lecture, Dr. Bayley indicated that the INESSS-ONF Guideline for Rehabilitation after Moderate and Severe Traumatic Brain Injury engaged users and relied on systematic evidence in all stages of the development. Importantly, the guidelines have unique features that respond to users' needs and can be navigated quickly using smartphones, tablets or computers to find recommendations, evidence summaries, implementation tools and measures of adherence and outcomes. Finally, Dr. Bayley encouraged the audience to take advantage of other available online Canadian resources (**Fig. 3**).

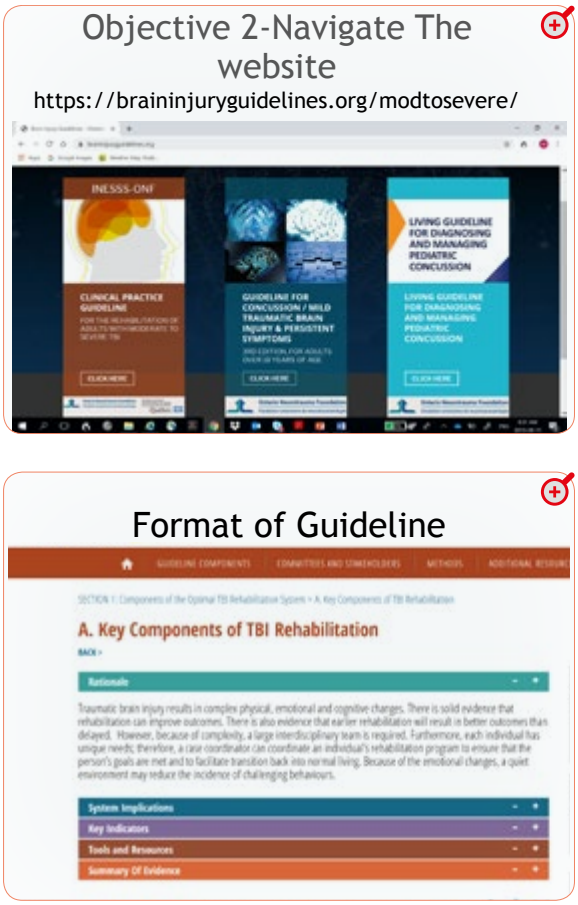


Fig. 2. The brain injury guidelines website and the format of the INESSS-ONF

Fig. 3. The best TBI management practices and resources available from Canada

Cognitive disorders after stroke: classification and perspectives for therapy

Michael Brainin

Professor of Neurology, Chair/Director, Department of Clinical Neuro- sciences and Preventive Medicine Danube University, Krems, Austria

ABSTRACT:

Disorders of cognition (neurocognitive disorders) following stroke occur between 7% in population-based studies of first-ever stroke patients and 41% in hospital-based studies which includes recurrent strokes.

Milder forms of cognitive deterioration following stroke were found in between 22% and 84% of patients, depending on the definition, testing, and time of the investigation. Incidence rates are 2-3% while increasing annually at linear rates. Importantly, milder forms can also be quite disabling and hinder rehabilitation and reuptake of occupational and social roles.

Probably all stroke patients are at risk of suffering from cognitive deterioration but some risk factors are more important than others such as the location of the stroke, initial stroke severity, previous strokes, level of pre-stroke cognition and presence of vascular risk factors.

Genetic and inflammatory biomarkers are under investigation but observational data suggest that high levels of interleukins and C-reactive protein have predictive value.

Cognitive and brain reserve can protect against cognitive deterioration and depends on education, leisure activities and social interactions. Moreover, the diagnosis of post-stroke cognitive deterioration (mild neurocognitive disorder) varies according to test instruments used. Usually, a short bedside test is used and an extended neuropsychological test battery is applied later. Variations also result from speech disturbances, emotional disorders such as depression.

CT and MRI confirm the diagnosis and provide additional information on the location and size of the infarct, previous infarcts, white matter lesions, microbleeds, and brain atrophy.

Management focuses on prevention and includes cognitive training and modification of risk factors. Lifestyle modifications have been shown to be beneficial in preventing cognitive decline in persons at risk of dementia. To date, exploratory drug trials and case series have shown promising effects in stroke patients and are under further investigation.

For future clinical use, there are two options: one is to develop a highly selective drug which inhibits epigenetically triggered factors involved

in harmful activation of immunomodulatory pathways and thus protects against a decline in a yet to be specified, high-risk population.

In these patients, the high risk is defined by raised levels of circulatory markers or brain lesion analysis defined from neuroimaging.

The other perhaps more promising option is based on multiple factor causation of cognitive decline triggered by a cascade of events known to be triggered by ischemic lesions. For this approach, a less specific but multimodal approach therapy can be applied to all post-stroke patients who are at risk for developing a post-stroke cognitive disorder.

Currently, efforts for both models are underway. Immune-modulatory substances known to foster remyelination in other neurological diseases are currently being tested (in a very narrow indication) and on the other hand, the multimodal neuromodulator Cerebrolysin is being tested (in a very broad indication) for prevention of post-stroke cognitive disorders in a multicentre trial.

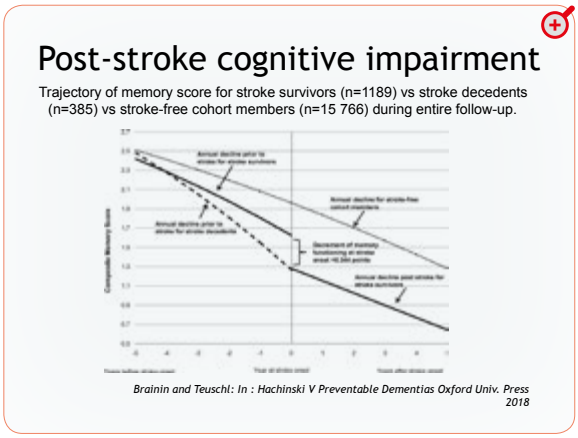
The topic of Dr. Brainin's lecture was the recent progress made in the field of post-stroke cognitive decline. He overviewed a definition and pathology, a new development in high-field MR imaging, longitudinal observations and trajectories of cognitive decline in whole populations, therapeutic time window and multi-domain interventions.

The definition of major and minor neurocognitive disorder (NCD) was formulated by Diagnostic and Statistical Manual of Mental Disorders (DSM5), which by itself is a good progress; until recently, cognitive decline was not considered a disease. This has blocked the licensing of new therapies in this important area. The definition of major NCD consists of a significant cognitive decline that interferes with independence. The definition of mild NCD projects moderate cognitive disorder with no interference with independence. Both are unrelated to delirium or other mental disorders. The cognitive deterioration after stroke can be underlined by several factors, like small vessel disease, strategic infarct, preexisting vascular/vessel damage, preexisting Alzheimer disease. The recently obtained high-resolution imaging data of progressing small vessel disease show hundreds of small lesions throughout the cortex (Van Veluw et al., 2017). These important pathological features are not detectable using lower resolution MR and have profound effects on cognition and impact also remote brain regions.

The strategic infarcts related to cognitive decline are mostly localized in the thalamus, parietal cortex, deep central regions, frontoconvex and cerebellar region. In the case of pre-existing vascular damage, two avenues can lead to cognitive decline. The first is cerebral microangiopathy leading to grey and white matter lacunes. The second is the amyloid-related microangiopathy leading to cortical amyloid arteriopathy related bleeds and microinfarcts. The pre-existing Alzheimer's disease is also a quite frequent cause of cognitive decline after stroke. In this case, a stroke accelerates the clinical presentation of Alzheimer's disease. Stroke and dementia are tightly related. This is why we say that currently, the best Alzheimer's disease prevention is stroke prevention. Statistically, 1 patient in 10 already has dementia when a stroke occurs, 1 patient in 10 will develop dementia after a first-ever stroke, and 1 in 3 patients will develop dementia with stroke recurrence. The typical pathological changes in patients with cognitive decline are lacunar infarcts, microinfarcts, white matter changes, hippocampal atrophy, and sclerosis. There is also an overlap with AD pathology featuring prominent amyloid plaques and neurofibrillary tangles. In some stroke patients, there is a pathological activation seen in the hippocampus on fMRI images. While infarcts occur very rarely in the hippocampus in isolation, this activation

appears to be the remote and delayed effect of the infarcts localized in the basal ganglia. Often, the personality changes in stroke patients occur later after discharge home and are not seen as a consequence of stroke. This is also a window of opportunity for the preventive treatments, suggested Dr. Brainin.

The large cohort studies give us a unique insight into the relationship between progressing cognitive impairment and stroke. For example, it was shown that progressing cognitive decline can be used as a predictor of future stroke. The reversal of modifiable risk factors was shown to reduce risk of stroke by 20% (**Fig. 1**).



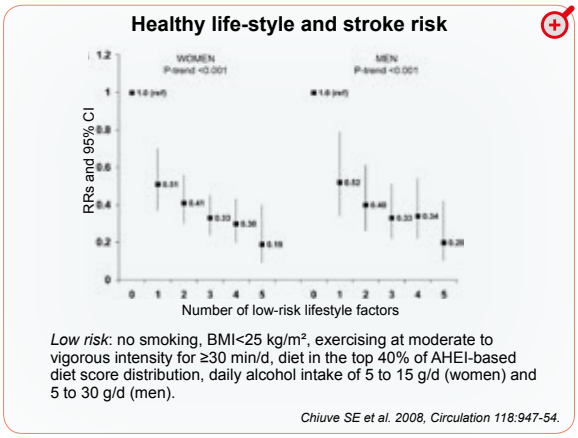
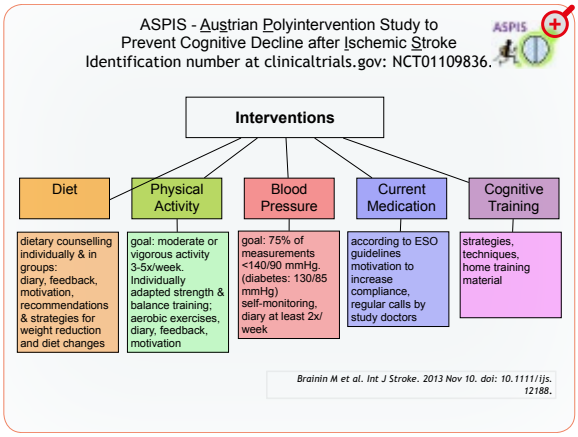


Fig. 1. The relationship between cognitive decline, modifiable risk factors and stroke can help in prevention of both stroke and dementia

These population observations gave an impulse for designing preventive studies, e.g. the Finger study (Ngandu et al., 2015). The aim of the study was to reduce cognitive impairment in an at-risk population (vascular risk and risk of developing Alzheimer's disease) through a 2-year multidomain lifestyle intervention including nutritional guidance, physical activity, cognitive and social activities, and intensive monitoring and management of metabolic and vascular risk factors (hypertension, dyslipidemia, obesity, impaired glucose tolerance). The primary outcome was a comprehensive neuropsychological test battery (NTB). Patients that underwent all those interventions had a significantly improved NTB score in comparison with the control group. A similar approach was applied to the stroke population by Austrian investigators in the ASPIS study (**Fig. 2**).



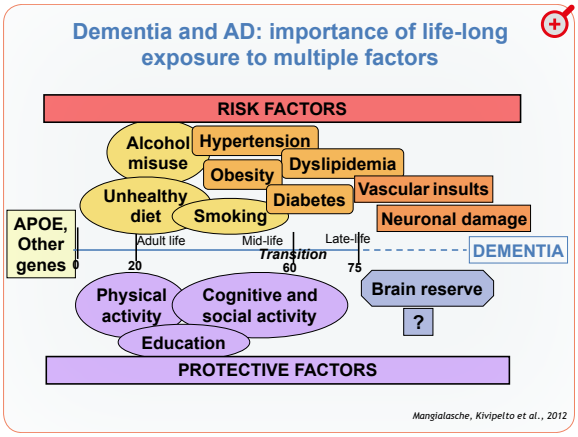


Fig. 2. The ASPIS study for prevention of cognitive decline after stroke and the complex entanglement of risk factors relevant for prevention of the cognitive decline in stroke patients

Although this particular study did not show statistically significant effects of the interventions, Dr. Brainin stated that the preventive approaches are important and should be further studied.

Regarding current developments in pharmacological approaches, Dr. Brainin mentioned two prominent avenues of drug development. Firstly, we can go for the highly selective (unimodal) drugs based on yet unknown biomarkers to identify high-risk patients. Such an intervention would aim to block the harmful activation of a specific immunomodulatory pathway or activate a specific repair mechanism. This approach could be applied to highly selected post-stroke patients. The alternative pathway can use a less specific multimodal approach. It can be applied to all stroke patients. In this case, there is no need for a specific biomarker. Such a treatment would aim to affect multiple causation factors at the same time. The use of biomarkers (SPECT imaging) for predicting the response to cognitive therapy was recently studied (Jenkins et al., 2019) in TBI patients. The study showed that patients with severe TBI and cognitive deficits responded positively to methylphenidate, a stimulant with dopaminergic effects. Randomized application to methylphenidate had the best effects in patients with low but not normal dopamine transporter binding (change in choice of reaction time, p=0.002). Another example is the ongoing multicenter POSTCODE-C study (A randomized, placebo-controlled multicenter study on the efficacy of Cerebrolysin vs Placebo on Post-Stroke-Cognitive Impairment) performed by the group of Prof. Muresanu. The study employs a 30 ml daily dose of Cerebrolysin in 6 centers. It aims at the inclusion of 2 x 145 stroke patients, with endpoints at months 6 and 12. The primary objective is to assess the efficacy of Cerebrolysin versus placebo upon a battery of co-primary neurocognitive outcome scores at 6 and 12 months after baseline measure. The secondary objectives are to assess the efficacy of Cerebrolysin versus placebo upon a battery of the co-primary neurocognitive outcome scores at 3 months after baseline as well as on neurological deficit, functional outcome, symptoms of anxiety and depression, drug safety and quality of life at 3, 6, and 12 months after baseline.

Safety and efficacy of Cerebrolysin in recanalization therapy – a case series

Maksim Domashenko

Magnitogorsk Iron & Steel Works' Clinic, Magnitororsk; Botkin Municipal Hospital Moscow, Stroke unit, Moscow, Russia

ABSTRACT:

The strategic goals of treatment in the acute period of severe ischemic stroke (IS) are to reduce mortality and disability. The only proven approach to achieve these goals is to use different reperfusion methods: i.v. rtPA thrombolysis, thrombectomy, or a combination of methods in a fairly narrow therapeutic time window. One of the contemporary scientific vectors is the search for opportunities to increase the effectiveness of reperfusion therapy by combining it with various methods of neuroprotection.

Three cases of using Cerebrolysin in combination with recanalization therapy will be demonstrated. Patients suffering from acute ischemic stroke were transferred to the Botkin Municipal Hospital for thrombectomy after acute care in the primary hospital. Thrombectomy was performed by using a stent retriever (Solitaire ®) with aspiration. Within one hour after thrombectomy patients were treated with the neuroprotective drug Cerebrolysin (30 mL). Treatment with Cerebrolysin was continued once daily for another nine days. NIHSS and mRS were assessed at arrival and discharge 10 days post-stroke. Cerebrolysin was well tolerated, adverse events were not detected and all recovery rates were acceptable.

These cases demonstrate that the combination of Cerebrolysin and comprehensive recanalization treatment was safe and further research seems feasible.

Dr. Domashenko began his presentation with an overview of the evolution of recanalization therapy in ischemic stroke patients (**Fig. 1**).

According to AHA/ASA 2018 clinical practice guidelines in stroke, depending on the neurological status of a patient (impairment level) and the time elapsed after stroke, it is recommended to use one of several strategies for rescuing ischemic penumbra. In adult patients with NIHSS < 6 (mild stroke) and time from stroke below 4.5 hours, one can use rtPA (after CT scan). In patients with NIHSS equal to or higher than 6 (moderate stroke), one can combine rtPA with thrombectomy (after CT and CTA scan) for up to 4.5 h post-stroke. In patients with moderate stroke, between 4.5 and 6.0 h post-stroke, it is recommended to use thrombectomy (after CT and CTA scan). Patients with moderate or severe stroke fulfilling the DAWN or DEFUSE 3 studies criteria, can be reperfused with thrombectomy in the therapeutic window extending above 6 h post-stroke (after CT, CTA, and CT Perfusion scanning).

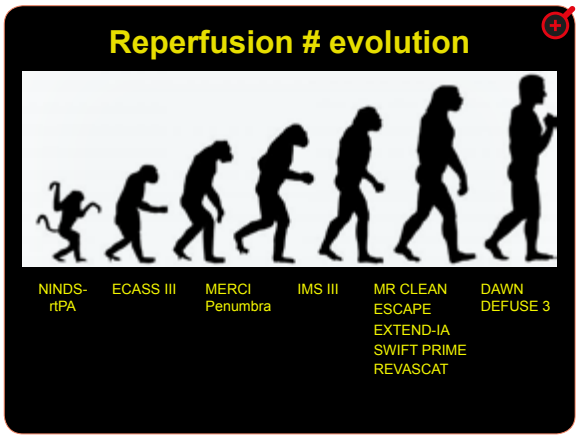


Fig. 1. The evolution of recanalization therapy in ischemic stroke patients

The idea of using a neuroprotective strategy together with reperfusion is not new, indicated Dr. Domashenko. It is also a reasonable idea as both strategies could complement each other for improved outcomes. However, in clinical practice, it doesn't work as expected. For example, the combination of rtPA with Cerebrolysin (CERELYSE study) showed significant improvement in NIHSS during 30 days post-stroke but failed to show the improvement at longer-term observation (mRS at day 90). Dr. Domashenko wanted to combine Cerebrolysin and thrombectomy to see if this particular combination would bring more benefits to the ischemic stroke patients. The idea was conceived during the meeting organized at his stroke unit in Moscow with Prof. Michael Chopp. Dr. Domashenko became interested in the data showing that Cerebrolysin prevents the accumulation of fibrin in the microvasculature counteracting the inflammatory cascade and protecting the blood-brain barrier in the ischemic stroke and TBI model (see Fig. 1 of Dr. Chopp's lecture). In light of these results, it made sense to try and use Cerebrolysin for supporting recanalization in selected ischemic stroke patients.

The first patient treated with Cerebrolysin was a 63 years old female with medical history of atrial fibrillation (AF) and time-to-door (TTD) 290 min.

The patient was severely impaired with NIHSS 18 (presenting hemiplegia and total aphasia). The treatment started with rtPA and subsequent thrombectomy followed by 30 ml Cerebrolysin (**Fig. 2**).

The combination of reperfusion with Cerebrolysin (30 ml for 10 days) was safe. The early outcome at day 10 was NIHSS 6 and mRS 2. The patient recovered successfully with the outcome score of mRS 1 after 90 days.

The second case presented was a 74 years old female with cardioembolic IS and a medical history of AH, AF (on rivaroxaban), and type 2 diabetes. TTD = 320 min and impairment level NIHSS 17 at admission (with hemiplegia, hemianesthesia, neglect). IS characteristics included CT ASPECTS 9 score and CTA showing right MCA M1 occlusion. The treatment, in this case, involved thrombectomy (aspiration + Solitaire) + Cerebrolysin 30 ml for 10 days. TTR was 35 min. Also, in this case, the combination of Cerebrolysin with thrombectomy proved at least safe. The patient recovery at 10 days denoted NIHSS 5, and mRS 2. After 90 days the mRS score stayed 1.

The final case was also a female patient, 43 years old with IS due to coagulopathy and medical history of oral contraceptive drug administration. TTD = 330 min. The patient was severely impaired with NIHSS 20 (hemiplegia, total aphasia). CT scan showed ASPECTS 7 score and CTA showed left ICA and MCA M1 occlusion. The applied treatment consisted of thrombectomy (aspiration + Solitaire) + Cerebrolysin 30 ml for 10 days. TTR 55 min. After the treatment, on day 10, the impairment level was at NIHSS 12 and the outcome at mRS 3. After 90 days of rehabilitation, the mRS score equaled 2.

These three cases showed that the combination of Cerebrolysin with thrombectomy is at least safe. Regarding the efficacy of this combination,

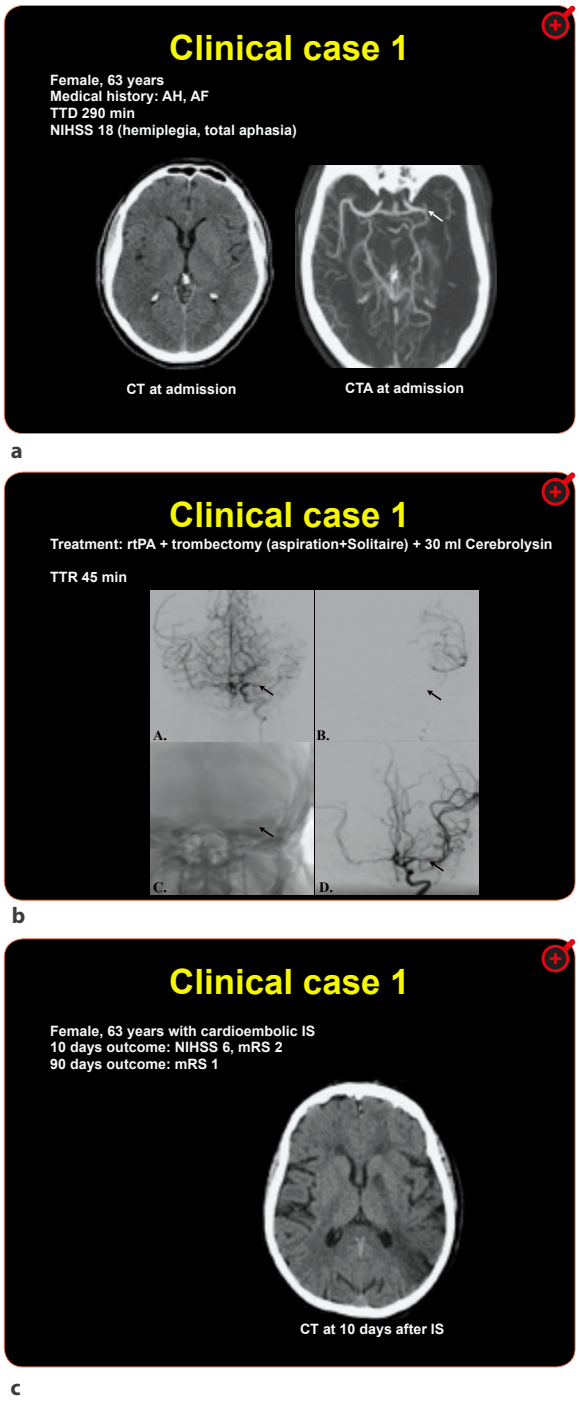


Fig. 2. The first case study of Cerebrolysin combination with thrombectomy: initial findings (a), technical benefit after treatment (b), and 10 days CT (c)

the clinical trials are extremely needed, said Dr. Domashenko. One interesting idea for the future study would be to combine rtPA and thrombectomy with Cerebrolysin in the real-life environment of the Russian clinics. For example, rtPA could be administered in the primary stroke center, while Cerebrolysin could be administered afterward, before a patient reaches the comprehensive stroke center and receives thrombectomy (**Fig. 3**).

Concluding his lecture, Dr. Domashenko stated that from his point of view Cerebrolysin is much more than a neuroprotective drug. It is a vascular protector with additional neurorepair properties. It seems, that the combination of Cerebrolysin with the current gold standard in reperfusion (rtPA and thrombectomy) is safe. Both, the pharmacological profile of the drug and clinical experience with Cerebrolysin in the treatment of ischemic stroke warrant further clinical development.

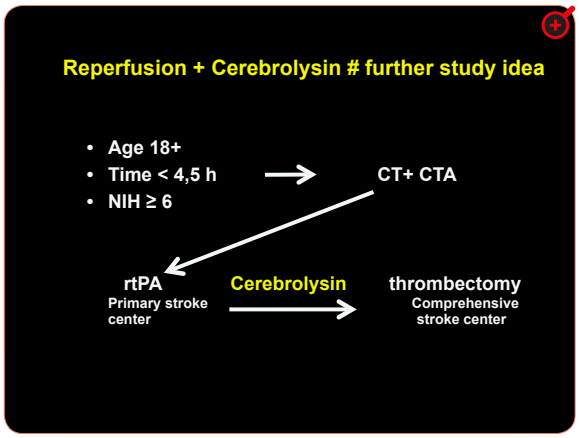


Fig. 3. The idea for the future study evaluating safety and efficacy of combination treatment rtPA + Cerebrolysin + thrombectomy of ischemic stroke patients in the real-life clinical environment

Possible synergistic effects of rtPA and Cerebrolysin in patients with acute ischaemic stroke

Zdravka Poljakovic

Neurological Intensive Care Unit, Department of Neurology, University Hospital Zagreb, Croatia

ABSTRACT:

Thrombolytic therapy with rtPA remains a „golden standard" for treating acute ischaemic stroke (AIS). In a clinical setting, though, thrombolytic treatment results in recanalization in only 30% of patients, and in some of them increases the risk of serious complications.

Cerebrolysin however, showed several levels of neuroprotection after thrombolysis, due to its effect on the blood-brain barrier, without influencing the fibrinolytic properties of the drug.

Considering this fact, we performed a prospective study on patients with acute ischemic stroke after thrombolytic therapy with or without endovascular recanalization therapy, but in any case without clinical improvement in the first 24 hours. The patients were divided into two groups – study group of patients who received Cerebrolysin during at least 14 and no longer than for 21 days, and a control group of matched patients who did not sign the informed consent for Cerebrolysintreatment. Patients in both groups had baseline NIHSS of >8. We compared outcome after 7 days of treatment (NIHSS), at discharge and after 90 days (mRS). We included altogether 18 patients in the Cerebrolysin group, and 17 matched controls patients.

An interim analysis showed some differences in outcome considering the mortality rate, and lower mRS in favor of the Cerebrolysin group, without any differences in complications rate. The final results of our study will be presented in this lecture.

Based on our results, Cerebrolysin is considered safe for patients with acute stroke after thrombolytic therapy with or without thrombectomy, and there is a certain benefit in the 90 days outcome in the Cerebrolysin patients' group.

The idea of using Cerebrolysin as an add-on to recanalization therapy in stroke patients was supported and further discussed by Dr. Poljakovic. In her focus are pharmacological effects of Cerebrolysin that seem to be complementary to those observed in the clinic after treatment with rtPA.

It is well known that the substances produced endogenously may play positive and negative roles depending on the physiological context, time of production, distribution and the dosage. The same concerns tPA, which is mainly produced in the hippocampus, hypothalamus, thalamus, amygdala, cerebellum, but also generally in parenchymal brain cells. It is also upregulated by the ischemic conditions.

rtPA – the drug – has revolutionized the treatment of stroke patients. It is used in recanalization of all types of stroke and it is now supported or sometimes substituted with thrombectomy. Unfortunately, even successful recanalization does not guarantee clinical progress. The hypo- and hyperperfusion, as well as reperfusion injury, can often limit the recovery of a patient. These post-recanalization complications are related to the function and structure of the BBB which is compromised by the stroke itself and by the recanalization procedures.

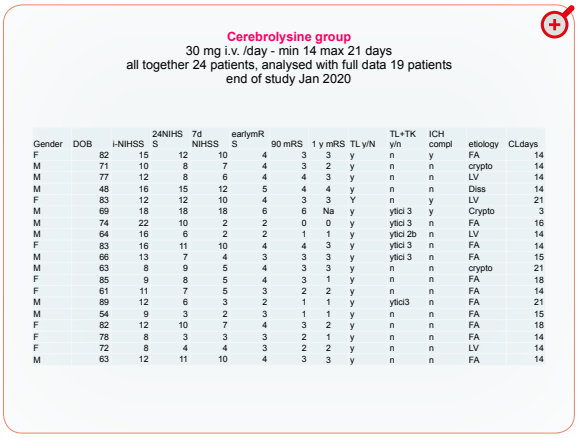
Cerebrolysin is a substance with neuroprotective and neurorestorative properties. The results of several studies with Cerebrolysin in the ischemic stroke showed positive treatment effects in the more severely affected stroke population. Cerebrolysin was also shown to protect and repair BBB and to stimulate the endogenous tPA. This crosstalk of substances denoted the backdrop for the idea to study Cerebrolysin as an add-on to recanalization therapy. It assumed that Cerebrolysin could improve the outcomes in severe stroke patients who do not show clinical improvement (≥ 2 points in NIHSS) after recanalization therapy (either with rtPA alone or rtPA and thrombectomy) in the first 24 hours after the treatment. The severity of stroke in the study was determined by the initial NIHSS read. The outcome was measured in early mRS and follow up mRS – after 90 days and 1 year. Secondary outcome measures chosen were a hemorrhagic transition of ischaemic stroke and death.

The inclusion criteria were: acute ischaemic stroke, NIHSS ≥ 8, recanalization therapy (TL alone or TL+TC), signed informed consent and Cerebrolysin given up to 24 hours after stroke onset. Patients who gave no consent for Cerebrolysine therapy, with renal failure and medical history of depression, allergy, and on MAO inhibitors were excluded. The patients included in the control group had a similar clinical profile to the study group, including unsuccessful recanalization.

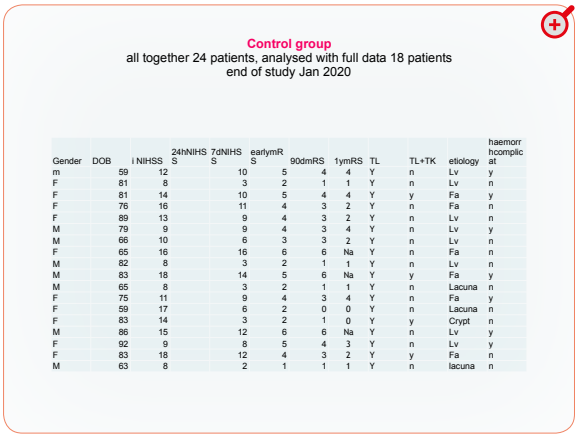
These patients did not give their consent for treatment with Cerebrolysin. Cerebrolysin was given for a minimum of 14 and a maximum of 21 days. Overall, patients included in the study were well matched between the groups (**Fig. 1**).

The initial NIHSS score was identical in compared groups, with a mean value of 12.5 (8-22) and 12.4 (8-18). Both groups of patients had moderate to severe strokes. 7 days NIHSS was 6.6 for Cerebrolysin and 8.1 for Control group (without a statistically significant difference). The comparison of mRS scores after 90 days showed a slight advantage of the Cerebrolysin group in comparison to the Control group (without statistical significance). The rate of death in the Cerebrolysin group was significantly lower (5%) in comparison with Control (17%). Similarly, the rate of hemorrhagic transformation was significantly higher in the Control group.

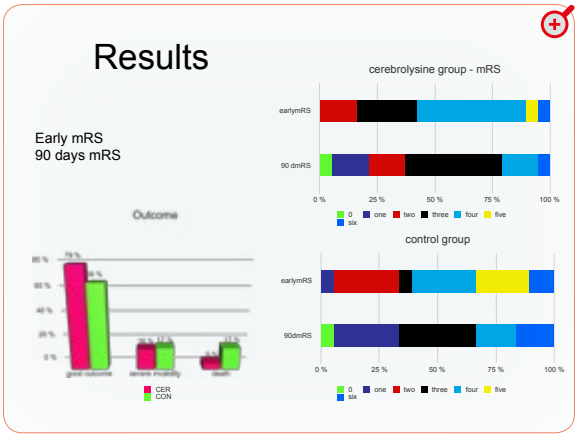
In conclusion, there were no safety issues concerning Cerebrolysin treatment which is important for future fine-tuning the treatment window and dosage optimization studies. The positive trend for improved outcomes after treatment with Cerebrolysin was recorded. Importantly, the clear benefit of Cerebrolysin in reducing the hemorrhagic transformation as well as the mortality rate was evident. The results of the full analyses will be published in 2020. In light of these promising results, the investigators plan a new study to assess the efficacy and safety of Cerebrolysin in subarachnoid hemorrhage patients.



Gender	DOB	i-NIHSS	24NIHSS	7d NIHSS	earlymRS	90 mRS	1 y mRS	TL y/N	TL+TK y/n	ICH compl	etiology	CLdays
F		82	15	12	10	4	3	3	y	n	y	FA	14
M		71	10	8	7	4	3	2	y	n	n	crypto	14
M		77	12	8	6	4	4	3	y	n	n	LV	14
M		48	16	15	12	5	4	4	y	n	n	Diss	14
F		83	12	12	10	4	3	3	Y	n	y	LV	21
M		69	18	18	18	6	6	Na	y	ytici 3	y	Crypto	3
M		74	22	10	2	2	0	0	y	ytici 3	n	FA	16
M		64	16	6	2	2	1	1	y	ytici 2b	n	LV	14
F		83	16	11	10	4	4	3	y	ytici 3	n	FA	14
M		66	13	7	4	3	3	3	y	ytici 3	n	FA	15
M		63	8	9	5	4	3	3	y	n	n	crypto	21
F		85	9	8	5	4	3	1	y	n	n	FA	18
F		61	11	7	5	3	2	2	y	n	n	FA	14
M		89	12	6	3	2	1	1	y	ytici3	n	FA	21
M		54	9	3	2	3	1	1	y	n	n	FA	15
F		82	12	10	7	4	3	2	y	n	n	FA	18
F		78	8	3	3	3	2	1	y	n	n	FA	14
F		72	8	4	4	3	2	2	y	n	n	LV	14
M		63	12	11	10	4	3	3	y	n	n	FA	14



Gender	DOB	i NIHSS	24hNIHSS	7dNIHSS	earlymRS	90dmRS	1ymRS	TL	TL+TK	etiology	haemorrhcomplicat
m		59	12	10	5	4	4	Y	n	Lv	y
F		81	8	3	2	1	1	Y	n	Lv	n
F		81	14	10	5	4	4	Y	y	Fa	y
F		76	16	11	4	3	2	Y	n	Fa	n
F		89	13	9	4	3	2	Y	n	Lv	n
M		79	9	9	4	3	4	Y	n	Lv	y
M		66	10	6	3	3	2	Y	n	Lv	n
F		65	16	16	6	6	Na	Y	n	Fa	n
M		82	8	3	2	1	1	Y	n	Lv	n
M		83	18	14	5	6	Na	Y	y	Fa	y
M		65	8	3	2	1	1	Y	n	Lacuna	n
F		75	11	9	4	3	4	Y	n	Fa	y
F		59	17	6	2	0	0	Y	n	Lacuna	n
F		83	14	3	2	1	0	Y	y	Crypt	n
M		86	15	12	6	6	Na	Y	y	Lv	y
F		92	9	8	5	4	3	Y	n	Lv	y
F		83	18	12	4	3	2	Y	y	Fa	n
M		63	8	2	1	1	1	Y	n	lacuna	n



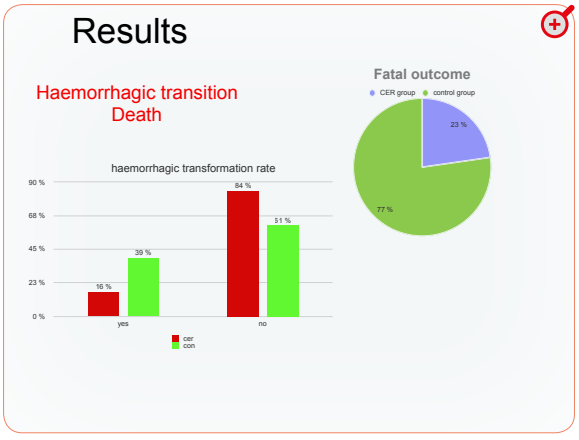


Fig. 1. The results of the study evaluating the safety and efficacy of Cerebrolysin in ischemic stroke patients without clinical improvement 24 h after successful recanalization

New hope for chronic stroke patients – The IMPULSE study

Andreas Winkler

Department of Neurological Rehabilitation, Klinik Pirawarth, Bad Pirawarth, Austria

ABSTRACT:

Stroke is the leading cause of long-term disability worldwide. The immense burden of stroke-related disability demands for new approaches in neurorehabilitation. Encouraging results have been reported by noninvasive brain stimulation (NIBS), specifically transcranial direct current stimulation (tDCS), which modulates cortical excitability to facilitate motor learning.

The neurotrophin BDNF (brain-derived neurotrophic factor) is seen as a relevant effector of tDCS due to its role in synaptic plasticity, learning, and memory. Accordingly, anodal tDCS (atDCS) over M1 induces a form of long- term synaptic plasticity that requires activity-dependent BDNF secretion.

Cerebrolysin is a neuropeptide preparation that has shown to promote motor recovery in stroke patients and to increase BDNF levels in patient sera. Animal models have shown increased neuronal sprouting and synaptic plasticity after Cerebrolysin administration.

In the IMPULSE study, we hypothesize that the combination of Cerebrolysin and atDCS will enhance the therapeutic benefit of a concomitant neurorehabilitation program, which includes a conventional rehabilitation protocol and task-oriented training.

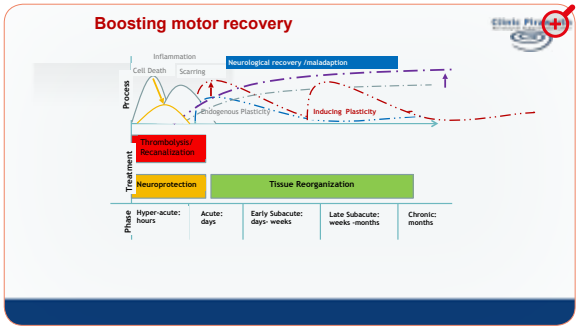
The IMPULSE study is a prospective, multi-center, randomized, double-blind study to assess efficacy and safety of neuroplastic intervention with Cerebrolysin and atDCS on motor function recovery in subacute and chronic stroke patients. The study will be performed at seven Austrian stroke centers with the first patient being enrolled in October 2019.

IMPULSE is part of VASCage-C, a competence center of the COMET program supported by public funding.

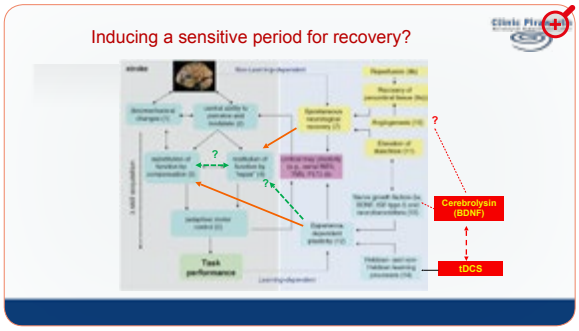
The last lecture of the meeting concerned the rehabilitation of stroke patients in the chronic (or post-acute) phase. Dr. Winkler is a Medical Director of the Klinik Bad Pirawarth specializing in long-term neurorehabilitation. He discussed the practiced and potentially new ways of improving the outcomes due to long-term neurorehabilitation. He also presented the new clinical project, the IMPULSE study, that is about to begin in October this year.

It is important to always try to improve clinical processes in stroke rehabilitation. Stroke is not only an acute killer but also a chronic and progressively disabling disease. It remains the second leading cause of death worldwide, with 5.5 million deaths attributed to it in 2016. The highest incidence rates occur in east Asia, followed by the Eastern European region (Feigin et al., 2019). There are still many challenges in stroke rehabilitation. The motor weakness/hemiparesis is seen in more than 80% of patients. 1/3 suffer from aphasia. 60% of patients with non-functional arms 1 week post-stroke do not recover. 10% develop PSD within 6 months. The effective neurorepair means to counteract all these problems are still lacking. Finally, there is no much time to apply effective neurorehabilitation strategies after stroke due to the short time window of dynamic changes in plasticity that could be targeted in the rehabilitation process. In predicting the effectiveness of rehabilitation efforts the "proportional recovery rule" was established (Winters et al., 2015). It states that up to 70% of patients (mild and moderate stroke) will recover about 80% of their motor functions. We are looking for treatments that would enhance the recovery above this 80% threshold for the majority of patients and help severely affected patients to join the successful recovery group. The development of such therapies requires knowledge about underlying biological mechanisms of recovery (**Fig. 1b**).

Effective acute treatment is a prerequisite of successful neurorehabilitation. Taking advantage of the relatively short time window of the spontaneous remission period (endogenous neuroplasticity period) lasting about 5-12 weeks is another priority.



a



b

Fig. 1. The timing of recovery phases (a) and the potential mechanisms underlying the induction of plasticity in the chronic stroke phase (b)

How to stimulate these processes effectively and safely is still an open question. Finally, how to induce plasticity processes in the chronic phase of stroke, beyond the period of spontaneous remission, remains to be learned. This topic is of special interest for Dr. Winkler and his institute because, on average, stroke patients arrive in his clinic 42 days after the stroke.

The neurotrophic factors play key roles in inducing plasticity processes. It was also shown that certain brain stimulation procedures (like tDCS) and pharmacological interventions (e.g. Cerebrolysin) stimulate neurotrophic regulation and neurotransmission in the brain. Hence, the idea of the clinical study exploring the combination of these approaches for motor rehabilitation of chronic stroke patients (**Fig. 1b**). The new data from experimental model of stroke by Zeiler's group from Johns Hopkins University (Zeiler et al., 2016) appear to support this concept. They showed that it is possible to re-induce the increased plasticity period (or sensitive recovery period) post-stroke

by administering another stroke with subsequent motor training rehabilitation. They also showed that the same can be done by replacing motor rehabilitation with Cerebrolysin immediately after the stroke. The underlying mechanism appears to be related to the stimulation of neurotrophic regulatory pathways, including the production of the brain derived neurotrophic factor (BDNF). Both Cerebrolysin and tDCS were shown to be potent stimulators of BDNF (**Fig. 2**).

The IMPULSE study brings the concept of the re-inducing sensitive recovery period in the chronic stroke phase to a practical clinical level. It combines tDCS and Cerebrolysin treatment with intensive motor rehabilitation of stroke patients. The design for the IMPULSE study was pre-tested by Dr. Winkler's group in the exploratory trial (Winkler et al., 2019 in press). 44 chronic stroke patients (>4 weeks from stroke onset) with impairment of upper extremity (UE) motor function (SAFE > 4, ARAT > 12, and subcortical ischemic stroke) were divided into 3 arms: Group A, receiving only daily task-specific training (minimum 30 minutes 5 days/week) over 2 weeks; Group B, receiving daily task-specific training plus anodal tDCS (20 minutes, 5 days a week) over 2 weeks; and Group C, receiving the triple-therapy consisting of daily task-specific training (minimum 30 minutes 5 days/week), anodal tDCS (20 minutes, 5 days/week) and daily administration of Cerebrolysin® 30 ml iv. over 2 weeks. The primary endpoint was the Action Research Arm Test-Score (ARAT) at day 14, determined as a proportional recovery score (PPR%). Although this was only an open observational study, the descriptive statistical analysis showed a signal confirming the accumulated benefit of the triple treatment concept in chronic stroke patients. The triple therapy improved their proportional recovery by three-fold (**Fig. 3**).

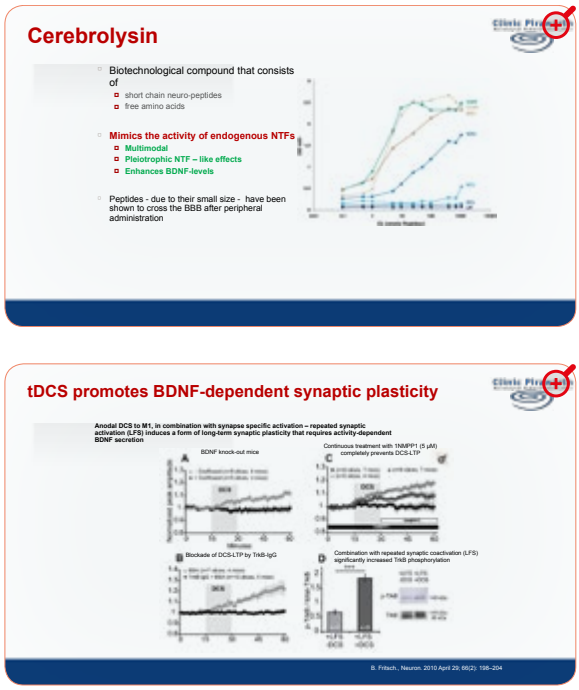
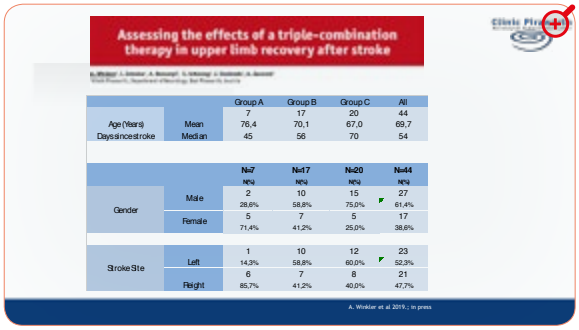


Fig. 2. Stimulation of neurotrophic regulation by Cerebrolysin and tDCS



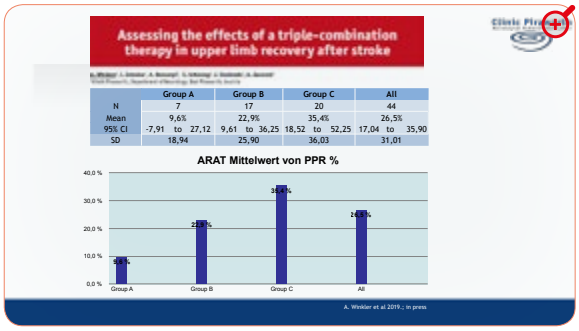


Fig. 3. The results of an exploratory trial investigating the motor rehabilitation of chronic stroke patients

These results prompted the design of a prospective, multi-center, randomized, double-blind study to assess efficacy and safety of neuroplastic intervention by Cerebrolysin and atDCS on motor function recovery in subacute and chronic stroke patients (the IMPULSE study). This is a publicly funded project within the Austrian VASC-age program. The pilot (phase II) trial will include 90 patients recruited in 7 Austrian sites and will run from October 2019 until Q4 2021. Pending the positive results of this trial, the IMPULSE II (phase III) is planned on a larger patient population. The pilot study design employs two arms assessing Cerebrolysin together with tDCS as an add-on to the routine motor rehabilitation regimen in comparison with placebo, sham tDCS and motor rehabilitation (**Fig. 4**).

Fig. 4. The design of the IMPULSE study

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.

EVER Neuro Pharma GmbH
Oberburgau 3
4866 Unterach
Austria
www.everpharma.com

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